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# THE TRAINING OF THE CANCEROLOGIST*

## THE PRESIDENT'S ADDRESS

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IN GOING over the now well-established literature of the past presidents' addresses, I find that a great variety of subjects has been explored. The recent trend has been in topics of education and its various ramifications, but little has been said about the need for training oncologists. As this is a problem which poses some questions which might be solved by members of this society, I have chosen the subject, "The Training of the Cancerologist."

As a member of a group treating cancer in its many forms, I am impressed by the fact that approximately 70 per cent of the cases seen in our practice have had previous treatment. For example, of the last 100 patients with malignant melanoma, seen by us since July, 1958, 94 per cent had had previous treatment: 45 per cent had biopsy only and then were referred for therapy; 6 per cent had what, in the light of our present knowledge, could be considered adequate therapy but there were recurrences; and 42 per cent must be considered to have been improperly treated. The same is true of the soft tissue sarcoma patients referred to our service at the Memorial Hospital. On the gastric service, we are seeing an increasing number of persistent and recurrent gastric cancer cases which have been inadequately treated but which can still be salvaged or palliated by further surgery. In reviewing this material, one is struck by the fact that over half of all previously treated cases have been treated by general practitioners, the rest by general surgeons (some, Board certified) with no specific training in the treatment of cancer, or by radiologists who do only occasional therapy.

Cancer is one of the few diseases in which early diagnosis and prompt and proper treatment make the difference between life and death. The 42 per cent of the previously mentioned series, who must be considered as having been poorly treated, were obviously hopeless on first consultation with us and subsequently lost their lives. Some of these could have been saved by proper initial treatment. It is a truism that should require no elaboration that the physician treating cancer should have an intimate and extensive knowledge of the biologic nature and behavior of the disease. This point is illustrated by the following case histories.

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Fig. 1. Photograph showing the tumor of the left thigh of a one month old child.

Figure 1 shows a one-month old child with a large tumor of the left thigh. He had been seen by a radiotherapist who advised that he receive 4 treatments of 200 r each, given tangentially. A distinguished pediatric surgeon was called in consultation and recommended that amputation be done when the child recovered from the jaundice which had followed hormonal therapy and transfusion. Finally, he was seen by a trained tumor specialist, who, knowing the natural history of the disease (hypertrophic hemangioma), recommended that no therapy be given, as the tumor would naturally regress. Fortunately, the child's leg was not deformed nor amputated, and Figure 2 shows the child at the age of four with the leg returned almost to normal.

Figure 3 shows a similar case, first seen at the age of eight and one-half months. The child had been referred for amputation of what was thought to be a malignant tumor. Figure 4 shows the child at the age of fourteen months, and Figure 5 shows the child at the age of seven years. No treatment was given because of the knowledge that the tumor would regress spontaneously. There are reports in the literature of major amputations done for such tumors.

Cancer is a relatively rare disease, as evidenced by the fact that cancer patients occupy only 7 per cent of the beds in the average general hospital in the United States. This material is even further diluted by division among the various departments or specialists. It is easy to see why the general surgeon, the internist, gynecologist, pediatric surgeon, urologist, dermatologist, etc., trained in general or university hospitals which are not particularly interested in the treatment of tumors, can have little experience or knowledge of the biologic history of this protean disease. In contrast with this wide distribution of cancer cases,

Fig. 2. Same child as in Figure 1 at the age of four.

Fig. 3. Photograph showing the arm of an eight and one-half month old child with hypertrophic hemangioma.

Fig. 4. Arm of the same child as in Figure 3 at the age of fourteen months.

Memorial Hospital admits 9 times as many as any general hospital twice its size in New York City. Thus, a resident spending three years at Memorial Hospital would have experience with cancer equal to twenty-seven years in a general hospital twice its size. Such concentrated training and material certainly should lead to a better understanding of the natural history of the disease and its proper treatment.

Fortunately, many of the patients who have had previous treatment are still salvageable. It is disturbing to note, however, the tendency for the highly trained specialist to apply to all forms of the disease the only method known to him. It is common for us to see the radiotherapist continuing treatment where viable cancer is evident along with radiation necrosis in the surrounding tissues. The surgical practice of taking multiple biopsies to determine operability, in the presence of an evident cancer, can only be condemned as showing a lack of knowledge of the na-

Fig. 5. Arm of the same child as in Figures 3 and 4 at the age of seven years.

Fig. 6. Large retroperitoneal liposarcoma.

ture of the disease. The so-called "second look" principle indicates that the first look was obviously inadequate and that the approach to the extirpation of the cancer had been timid. The principle of plucking nodes from a cancer-bearing area as one might pluck raisins from a bun shows complete disregard of the well-established procedure of block dissection. The extreme philosophies of the inexperienced, which are based on the behavior of cancer at either end of the normal distribution curve, lead either to the nihilistic attitude that all cancer is hopeless, or to the equally unrealistic position that the cancer patient can be salvaged by almost any minor procedure. The constant reiteration of these fallacious principles in the literature and in training centers has done the cancer patient a great disservice.

The cancerologist should have a knowledge of the standard procedures in cancer surgery and a familiarity with the effects of ionizing radiations, as well as an understanding of the chemotherapeutic and hormonal approaches. The great significance of the biologic approach to cancer therapy is embodied in this principle. Although the usual feeling is that such training would require the powers of the Trinity, practical teaching and research in cancer must be a single discipline. In which field the trainee chooses to practice is an unrelated problem. The following case histories indicate that knowledge of the basic principles of all disciplines is not beyond the comprehension of the ordinary mortal.

Figure 6 shows the operative specimen removed from a young woman, aged twenty-five, who was first seen in October, 1951. She had a huge tumor in the left upper quadrant of the abdomen. She had been under the care of her physician because of discomfort of ten months' duration. A nodule had been removed from her left neck and a diagnosis of metastatic liposarcoma had been made. A roentgenogram of the chest on admission showed a mediastinal mass. The abdominal mass was removed in November, 1951. The patient was then given radiation therapy, using supervoltage, to the mediastinum and the bed of the excised tumor. The neck lymph nodes were treated with orthovoltage, as was a mass in the left popliteal space. A node appeared in the right carotid lymph node region and was treated with orthovoltage. In 1953, further disease appeared in the right neck and in the upper mediastinum. In December, 1953, an exploratory laparotomy was done because of symptoms of intestinal obstruction, and Figure 7 shows the operative specimens of omentum, a segment of the small bowel and a segment of the transverse colon which were removed because of involvement with metastatic liposarcoma. In April, 1955, another area of disease was noted in the right neck and treated with radiation therapy. Since this time, the patient has remained well with no

evidence of any activity of the disease, a matter of five years. I feel certain that such successful combinations of radiation therapy and surgery are not uncommon in the experience of the members of this Society. This case illustrates the value of an over-all knowledge of both modalities of treatment, and their application by the same individual.

Figure 8 shows a male, aged fifty, with a sarcoma of the presternal region, who had been operated on eleven times by a surgeon in an effort to eradicate a fibrosarcoma. He finally gave up at this point, and referred the patient to our institution for treatment. The patient was still operable and possibly curable. Figure 9 shows the operative specimen. The patient is now well, approximately ten months, without evidence of recurrence.

The modern trend of the general hospital and the university hospital toward avoiding concentration of cancer patients and treating them on the various specialty services is the fault of the administrative professors who are the planners of graduate

Fig. 8. Photograph showing a sarcoma of the presternal region in a fifty year old male.

medical education. The tendency for superspecialism to take over training, with the resultant isolation of specialties, is aided and abetted by the rigidity of the qualifying boards, which strive to narrow the

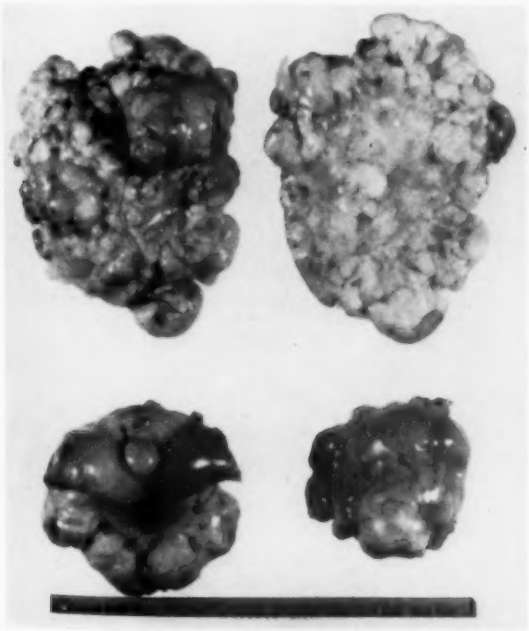

Fig. 7. Operative specimens of omentum, small bowel and transverse colon showing recurrent liposarcoma.

Fig. 9. Operative specimen from the patient shown in Figure 8.

scope of training and, consequently, experience in other fields. The unique character of the American Radium Society, in reality the oldest national scientific society primarily interested in the treatment of cancer, places it in the position to influence the trend of postgraduate medical education. Of the 342 members from the United States, 155 hold academic rank. There are 67 members certified by the Board of Surgery, 163 members certified by the Board of Radiology, and 24 members certified by the Board of Obstetrics and Gynecology. There are a number of members certified by the Boards of Internal Medicine, Dermatology and Syphilology, Urology, and Pediatrics. The membership includes physicists, dentists, and even a veterinarian. With this broad representation among the various certifying boards and the academic rank held by so many members, it is the most vital function of this Society, through its members, to train men in the broad knowledge of the disease and, therefore, in better understanding and treatment of the cancer patient.

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# THE PLACE OF INTERSTITIAL GAMMA-RAY EMITTERS IN RADIATION THERAPY*

## INDICATIONS—TECHNIQUE—EXAMPLES

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THE progress of radiation therapy in the last decade has been characterized by technical developments: the use of supervoltage, isotopes, moving field techniques and the application of more scientific dosimetry. At the same time very little has been done to develop further the techniques of interstitial irradiation which have proved to be so efficient in the treatment of a number of malignancies. The tendency in most radiation therapy centers is to abandon the use of radium in favor of external beam therapy even in cases where its efficiency has been proved by the good results obtained. Very few significant works in interstitial therapy have been published in recent years. The general tendency seems to be to exaggerate the disadvantages of the procedure rather than to look for improvement.

In spite of all the advances made in modern external beam therapy, there is a group of conditions which still is best benefitted by interstitial therapy, providing the indications, performance and dosimetry are properly considered. Undoubtedly, if more therapists become interested in developing the procedure, many of the objectionable features can be overcome or minimized. None of the objections against this technique of treatment are insurmountable if enough effort and ingenuity are put into the endeavor. More emphasis should be placed on the benefits of interstitial therapy and all its possible indications in order to exploit its therapeutic potentiality; only after this trial is a fair comparison with other means of therapy possible.

If one can avoid the haphazard procedures based only on empiricism, but still used today by many therapists, the whole field of interstitial therapy could be further developed on a more scientific basis with wider indications, less risk, and better results.

In recent years there have been several attempts to replace radium as a source of gamma rays for interstitial irradiation. $Co^{60}$, $Ce^{137}$, $Au^{198}$, $Ta^{182}$, and $Ir^{192}$ are the most important of these substitutes. As expected, there is no significant biologic difference between the radiation produced by these sources and that produced by radium. In some cases the malleability of the sources (tantalum wire and nylon threaded cobalt or iridium) offers some physical advantages from the standpoint of adaptability to the anatomic area to be implanted; in others, exposure from these sources is reduced to a minimum. They all have shorter half-life as compared with radium; therefore, added difficulties in dosimetry and source replacement are encountered. The flexibility of sources is not a desirable feature in all cases. We believe that rigid radium needles are better for the performance of a good implantation in the oral cavity, vulva, vagina, and in all cases where a cylindrical volume or any of the complex geometric pattern implants is indicated. The ideal approach is to have all types of sources available and to use the one most appropriate for each case. The flexible isotope sources are particularly suitable for extensive implants in flat, superficial areas where a large single plane is indicated, *i.e.*,

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chest wall recurrences from breast carcinoma, recurrences on the neck or groin after lymph node dissection, tumors of the skin, etc. The nylon threaded gamma-ray emitters offer the further advantages of reducing exposure to the operator.

As will be shown, in our institution an effort is being made to enlarge the indications for interstitial therapy by the use of complex geometric patterns of source distribution and by the implantation of bone and cartilage when involved by disease. Of course, these applications are possible only providing the proper distribution of sources and dosimetry are used. Uniformity and control of the dose are indispensable requirements if complications are to be avoided.

There exists another possible application of interstitial gamma therapy which is worth further exploration: the combination of external beam and interstitial therapy. There are many instances, especially in head and neck and some genital tumors, where combined therapy would present distinct advantages since the volume of normal tissues irradiated to very high dose levels would be reduced. With the increased use of 2 parallel opposing fields of supervoltage irradiation, the addition of interstitial treatment could reduce late radiation effects and avert complications in many cases.

This work represents the effort of our group to find the proper place for interstitial gamma therapy in the treatment of cancer. It is divided into four parts for better understanding.

## PART I. GENERAL PRINCIPLES

### A. ADVANTAGES OF RADIUM THERAPY (OR OTHER INTERSTITIAL GAMMA-RAY THERAPY)

Even with the increased use of supervoltage irradiation, interstitial gamma-ray therapy is the treatment of choice in many malignant tumors of the well-differentiated type which can be adequately covered by an implant. No other technique of irradiation will either offer the same advantages or yield the same results. Interstitial gamma-ray therapy is the only means of delivering supervoltage radiation where it is needed with maximum sparing of the normal tissues. The advantages can be categorized as follows:

1. *Accurate localization of the tumor and its extension.* Since all implantations should be performed under general anesthesia, an excellent opportunity is provided for examination by direct vision and palpation of the tumor.

2. *Irradiation is limited to the tumor bearing volume only* with proper adaptability of the shape. Irregular shapes of the irradiated volume may be devised to conform to the shape of the tumor; due to the sharp fall-off of the dose in interstitial therapy, the irradiation of the normal tissues is limited to a very short distance from the sources. No form of beam therapy can better spare the normal tissues.

3. *Supervoltage type of irradiation is used* with all its well-known advantages.

4. Due to the combination of (2) and (3) *a higher dose can be delivered safely* when required. This may be useful in the case of some of the well-differentiated squamous cell carcinomas and in most adenocarcinomas of the head and neck and genitalia. These tumors can be successfully treated by irradiation only by delivering a very high dose.

5. *Shorter treatment time.* This is a definite advantage in a busy department and generally represents less suffering and less economic stress to the patient.

Surprisingly enough, and in spite of these definite advantages, interstitial radium therapy has not had the acceptance that it deserves, probably because the disadvantages of the procedure have been overestimated. The most commonly mentioned disadvantages will be enumerated along with some of the possible ways of minimizing or avoiding them.

### B. DISADVANTAGES OF RADIUM THERAPY

1. *Irradiation of personnel and operator.* This is no doubt the main drawback of the procedure. By using proper technique and protective devices in and out of the operating room, together with adequate sharing of

the exposure among members of the staff, the radiation can always be maintained below the maximum permissible level.

Whenever indicated, the use of nylon threaded gamma emitters (Henschke[3]) and empty shafts which are filled with the proper isotope when the implantation is finished (Suit) will further help in diminishing the exposure. It is always more justifiable to expose ourselves and our personnel (within tolerance limits) in the performance of a highly curative procedure rather than in one using some radioactive isotopes where the chances of curing a patient are practically nil. In our institution where the facilities are not ideal, we seldom exceed the permissible tolerance level of irradiation by the proper handling of radium, adequate technique, protective devices and the sharing of exposure among several operators.

2. *Lack of versatility—limited indications.* It is true that the indications for interstitial therapy are limited but with sufficient ingenuity and the use of complex patterns in the arrangement of the sources, the number of cases properly treated by interstitial therapy can be considerably augmented. The use of surgery for the implantation is also a way in which to further increase the adaptability of the procedure.

3. *It is a surgical procedure.* This requires admission to the hospital, general anesthesia, special skill of the therapist, etc. Except for the general anesthesia in poor risk patients, all other objections are unimportant if the results are justifiable.

4. *More difficult dosimetry.* In a well organized department of radiation therapy, this is not a disadvantage. In most cases the type of implants to be used can be calculated in a short time with proper training. Elaborate equipment or special training in mathematics or physics is not necessary.

5. *Danger of implanting in or near bone or cartilage.* This is not a valid objection as will be shown later. In order to obtain the best results from interstitial therapy, the care in planning the distribution of sources, the technique for the performance of the procedure, and the care of the patient under treatment must follow strict rules, and the requirements should parallel those for major surgical procedures. It is unfair to expect good results from improvised plans or haphazard performances.

### C. Requirements for a Good Radium Implantation

1. *Adequate supply of radium needles.* The needles should be adequate in number, length, and in their linear intensity of radium (or other gamma-ray emitters) (Table 1). The proper supply of sources is a necessity if implantations with the required geometric pattern and which will deliver the dose in the proper time are to be carried out; we follow Regaud, Paterson,[6] and Martin[4] in prefering the treatment to be protracted between five to seven days. This protraction will give the best results with minimum damage to normal tissues.

2. *Proper indications.* In our Service, interstitial gamma-ray therapy is the treatment of choice of any malignant tumor which requires a localized high dose of radiation, providing it is still limited to an area which can be adequately covered by an implant, and the patient is a good risk for general anesthesia and is able to cooperate during the time that the needles are in place.

3. *A previously determined plan for the geometric arrangement of the sources.* A sketch of the lesion with the possible arrangement of sources is made the day previous to operation. This is used as a guide for the sources needed and as a model in the operating room. When a plan of definite geometric arrangement of sources is followed at operation, the dose delivered by the implant is always calculable.

4. *Careful operative technique.* If it is recalled that interstitial treatment is a precise treatment, it will be realized that general anesthesia is indispensable for the proper performance of the procedure. Proper asepsis, careful measurement and mapping of the patient, good anchorage of each needle by suturing, and good postoperative care are all important factors for successful treatment.

5. *Proper dosimetry.* Accurate calculation of the dose delivered in each case is essen-

TABLE I

PROPER STOCK OF RADIUM NEEDLES FOR ADEQUATE RADIUM IMPLANTATION (FOLLOWING PATERSON-PARKER)

*For Small Center*

| No. of Units | mg. of Radium | Active Length (cm.) | Actual Length (cm.) | Pt Filter (mm.) | mg./cm. | Total Amount (mg.) |
|---|---|---|---|---|---|---|
| 10 | .66 | 1 | 2 or less | 0.5 | .66 | 6.66 |
| 10 | .33 | 1 | 2 or less | 0.5 | .33 | 3.33 |
| 15 | 1.33 | 2 | 3 or less | 0.5 | .66 | 20.0 |
| 15 | .66 | 2 | 3 or less | 0.5 | .33 | 10.0 |
| 30 | 1.0 | 3 | 4.2 or less | 0.5 | .33 | 30.0 |
| 30 | 2.0 | 3 | 4.2 or less | 0.5 | .66 | 60.0 |
| 20 | 3.0 | 4.5 | 5.8 or less | 0.5 | .66 | 60.0 |
| 20 | 1.5 | 4.5 | 5.8 or less | 0.5 | .33 | 30.0 |
| | | | | | Total | 220 |

*Needles very useful but not indispensable*

| No. of Units | mg. of Radium | Active Length (cm.) | Actual Length (cm.) | Pt Filter (mm.) |
|---|---|---|---|---|
| 20 | 1.65 | 3 (Dumbbell)* | 4.2 or less | 0.5 |
| 15 | 1.15 | 3 (Indian club)† | 4.2 or less | 0.5 |
| 20 | 2.15 | 4.5 (Dumbbell)* | 5.8 or less | 0.5 |

* "Dumbbell" type of needles are "half-intensity" needles (.33 mg./cm.) with extra loading at each end. This extra charge when a row of needles is implanted makes a self crossing.

† "Indian club" type of needles are "half-intensity" needles with extra loading in one end only.

*For Large Center*

The distribution of the radium should be the same. The number of needles should be greater, especially of 2, 3, and 4.5 cm. active.

tial, in order to obtain consistently the best possible results with a minimum of complications and recurrences and to be able to transmit to others the benefit of one's experience. The means of calculation should be practical and realistic.

### D. DOSE-TIME RELATIONSHIP

The scheme of dosage used in our Service is as follows: In general, as a base line we follow Paterson-Parker's dosage system—7,000 r delivered in seven days for rather early tumors in a good tumor bed with good blood supply. This dose-time relationship is modified as follows:

1. The basic dose is decreased (6,000 to 6,500 r in six to seven days) in case of: (a) areas of poor tolerance (axilla, groin, anus, etc.); (b) proximity to sensitive structures (lens of the eye, etc.); (c) very old patients; and (d) large volumes of irradiation, especially involving large portions of bone, normal mucosa, or skin.

2. The basic dose is increased (7,500 to 9,000 r in seven days) in case of: (a) large masses of tumor such as in late tumors of the tongue, floor of the mouth, large and fixed lymph node metastases in the neck; and (b) more resistant types of tumors, such as adenocarcinoma of the salivary glands, etc.

### E. INDICATIONS

The main indications for interstitial therapy at the Division of Radiotherapy of the University of Maryland Hospital are as follows:

1. *Head and neck tumors.* In lesions of the *oral cavity*, radium alone is used in (a) most squamous cell carcinomas of early and medium extension; and (b) occasionally in some extensive lip lesions without bone

involvement. It is used in combination with external beam therapy in all large squamous cell carcinomas.

In lesions of the *oropharynx*, radium is used in combination with external beam therapy in some cases.

In lesions of *unusual anatomic locations*, *i.e.*, through bone and cartilage (ethmoid, anterior portion of nasal septum) radium is occasionally used after exenteration of the maxillary antrum or orbit.

For *neck* lesions, radium is used alone in cases of postoperative skin recurrences and in combination with external beam therapy for all medium and large lymph node metastases.

2. *Skin tumors*. Interstitial therapy for skin lesions is used in special cases only.

3. *Breast tumors*. Interstitial therapy is used for recurrences in the chest wall and as a complement to external irradiation in advanced tumors.

4. *Tumors of female genitalia*. Interstitial therapy is used in cases of tumors of the vulva and in groin metastases. It is always used as a complement to external irradiation in tumors of the vagina and in some cases of cervical stump tumors.

5. *Tumors of the anus*. Interstitial therapy is used for early or medium sized lesions of the perianal skin and in some early tumors of the anal canal.

6. *Bladder tumors*. Interstitial therapy is used mostly as a complement to external irradiation in infiltrating, large, well-differentiated tumors.

7. *Tumors of unusual sites*. Interstitial therapy is used in areas not usually implanted: recurrent rectal carcinoma in perineum, vagina and recurrences in the groin, and also in surgically exposed areas: vagina, parametrium, pharynx.

## PART II. TREATMENT OF ADVANCED SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK BY INTERSTITIAL RADIUM IMPLANTATION

### COMPLEX PATTERNS

Squamous cell carcinoma arising in the mucosa of the oral cavity and upper respiratory and gastrointestinal tract is highly curable by irradiation when the proper treatment is applied early. The treatment of early cases is fairly well established and will not be mentioned here. The discussion will be limited to the treatment of the more advanced stages of the disease.

These tumors exhibit characteristic and fairly constant patterns. Patients who come for treatment present different stages of evolution and extension of the disease, and can be grouped as follows:

1. *Advanced local extensions*. The primary tumor has progressed locally without lymph node metastases in the neck or with only small lymph node metastases in the first echelon of lymphatics (close to the primary). The lesion may invade bone, destroy adjacent organs, impair vital functions, and produce pain, infection and hemorrhage. This comprises a fairly large group of cases (Fig. 1 through Fig. 6).

2. *Advanced metastases in the neck*. In these patients the local extension of the tumor is not the striking feature of the disease; the metastases in the neck lymph nodes are the outstanding signs. In some cases the lymph node metastasis is single but locally advanced to large size, fixed to the vessels and/or bone (Fig. 7); in others the metastases are multiple and even bilateral. These tumors produce little discomfort to the patient. The primary tumor is sometimes early and even difficult to find, but it is more often fairly advanced.

3. *Advanced local disease and metatastases in neck lymph nodes*. Fortunately, this comprises a rather small group of patients. The disease is very advanced in both the primary site and in the lymph nodes (Fig. 8 and Fig. 9).

4. *Postoperative recurrences*. In some institutions this group of patients may be very large. Often the primary lesion has been controlled surgically and the recurrence is in the neck, with or without a radical neck dissection having been performed (Fig. 10). In other instances, the recurrence is in the area of the primary tumor. In many patients the actual disease does not

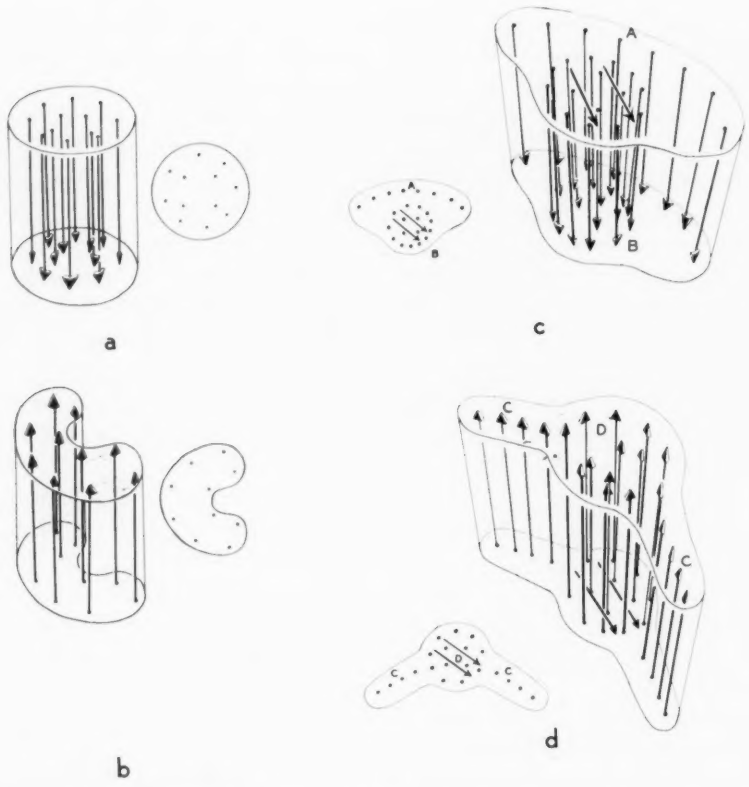


Fig. 1. *Extensive infiltrating carcinoma of the floor of the mouth.* This type of carcinoma carries a very poor prognosis especially when treated by external irradiation alone. A fair number of cases can be better controlled by interstitial therapy, provided the proper implant, often extensive, is used. Depending upon the extent of the disease and the direction of its spread, we have been employing the implants shown in schematic form:

(*a*) In cases of small and medium sized tumors without much infiltration or extension outside the local area, we use a single volume implant for anteriorly placed lesions and a double plane implant for those situated laterally (Fig. 2 and 3). The needles are implanted through the tongue. No crossing is used since this will only increase the reaction in the dorsum of the tongue without contributing to the treatment of the lesion. Silver clips are used to make certain that the position of the needles is correct (Fig. 3).

(*b*) If the tumor shows a definite infiltrating tendency, we add to the intraoral implant a submental one which generally is a curved double plane implant (Fig. 4) or another volume implant, depending upon the shape and size of the submental region. It has been our experience that these tumors have a marked tendency to recur in the submental area if treated by intraoral radium alone. This modification of technique is intended to treat the possible undetected extensions in that direction and has, so far, been efficient in all cases.

(*c*) If the lower gum is invaded by the tumor (including extension into the bone) a palisade-like, curved plane of 2 cm. active length needles (A) is added to the volume (B). This plane is implanted in the buccal and labial mucosa opposite to the extension of the tumor with appropriate margin (Fig. 13).

(*d*) In some patients with lymph node metastases in the submaxillary area or upper carotid chain, the implantation has to be extended to those areas, lateral wings (C) in the submaxillary areas being added to the submental volume (D). Figure 5 shows a case in which an implant of this type was used.

represent a true recurrence but rather residual disease or surgical seeding which reproduces the gross tumor shortly after operation.

5. *Distant metastases.*

The therapeutic management of all these patients is difficult, interesting, and, in many cases, rewarding. In most of the patients, the disease will remain localized above the clavicle for long periods of time and death is usually caused by local extension (infection, pain, functional impairment, and hemorrhage). In disease of this type which is still localized to a rather small

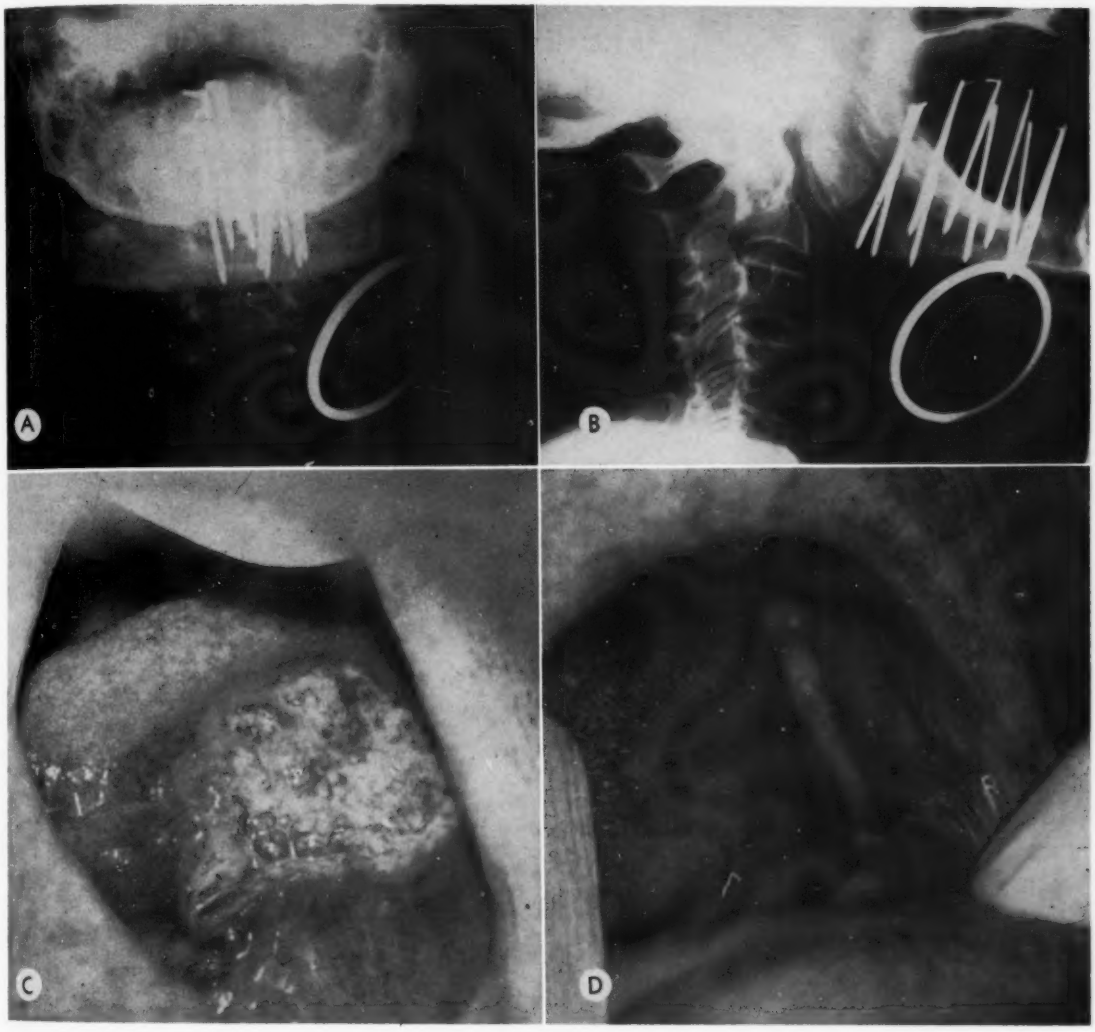


Fig. 2. W.S. 72 W M. *Squamous cell carcinoma of the floor of the mouth, extending to the undersurface of the tongue.*
(*A* and *B*) Double plane implant (dumbbell needles). The clips indicate the medial plane. The patient pulled out the whole implant after 3,500 r had been delivered in 88 hours. Treatment was completed by delivering a tumor dose of 4,000 r in 4 weeks by telecobalt therapy.
(*C*) Lesion before treatment and (*D*) more than 2 years after treatment.

segment of the body there should be little, if any, place for palliative treatment.

All the groups mentioned above deserve radical therapy aiming for a cure even if we know that the chances are that only palliation will be achieved in many cases. With radical treatment the palliation obtained is longer lasting, and some cases deemed hopeless may be brought under control. In fact, nothing less than radical treatment will control extensive, painful, ulcerated primary lesions and alleviate pain and hemorrhage. The local palliation generally achieved justifies radical therapy, even in patients with distant metastases, providing the general condition warrants it.

### General Considerations of Treatment

Most of the patients with advanced squamous cell carcinoma of the head and neck present a difficult problem of technique if they are to be treated properly. It

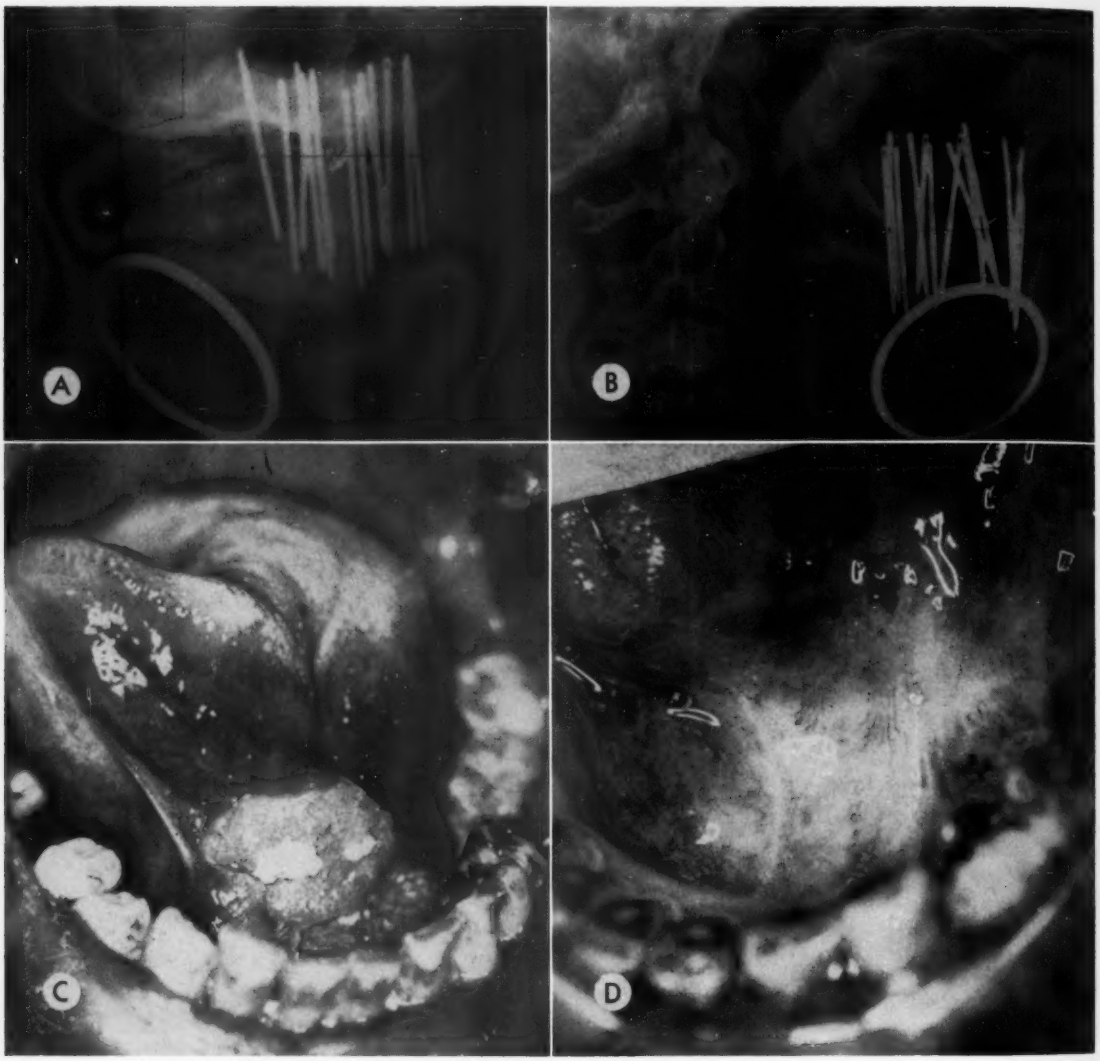


Fig. 3. L.L. 55 W M. *Squamous cell carcinoma of the floor of the mouth, mainly exophytic.*

(*A* and *B*) Single volume implantation without crossing using all half-intensity needles was performed through the tongue. Unless the tongue is fixed by the tumor invasion, it is anchored to the floor of the mouth by a mattress suture, avoiding the lesion. The silver clip marks the level of the lesion. If the roentgenograms show that the clip is not near the middle of the needle length, the implant is unsatisfactory and should be removed. The treatment is then completed by external irradiation. A dose of 7,000 r was given in 6 days.

(*C*) Lesion before treatment and (*D*) 2 years after treatment.

is well known that the majority of squamous cell carcinomas of the head and neck are tumors of moderate radiosensitivity. The dose required for their sterilization is high. In many cases the lethal dose is very close to the maximum tolerance of the normal tissues making up the tumor bed. If external beam irradiation is to be used, especially in cases with neck metastasis, the tolerance is limited by: (1) the large volume to be irradiated, including a great surface of skin, mucosa, bone, and cartilage; (2) the inevitable irradiation of vital structures of limited tolerance, such as larynx, spinal cord, lens of the eye, etc.; (3) the patient's reaction to therapy. The functional impairment due to epithelitis and mucositis produces pain, dysphagia, suppression of salivary flow, etc. In extreme cases, discomfort or starvation may necessitate cessation

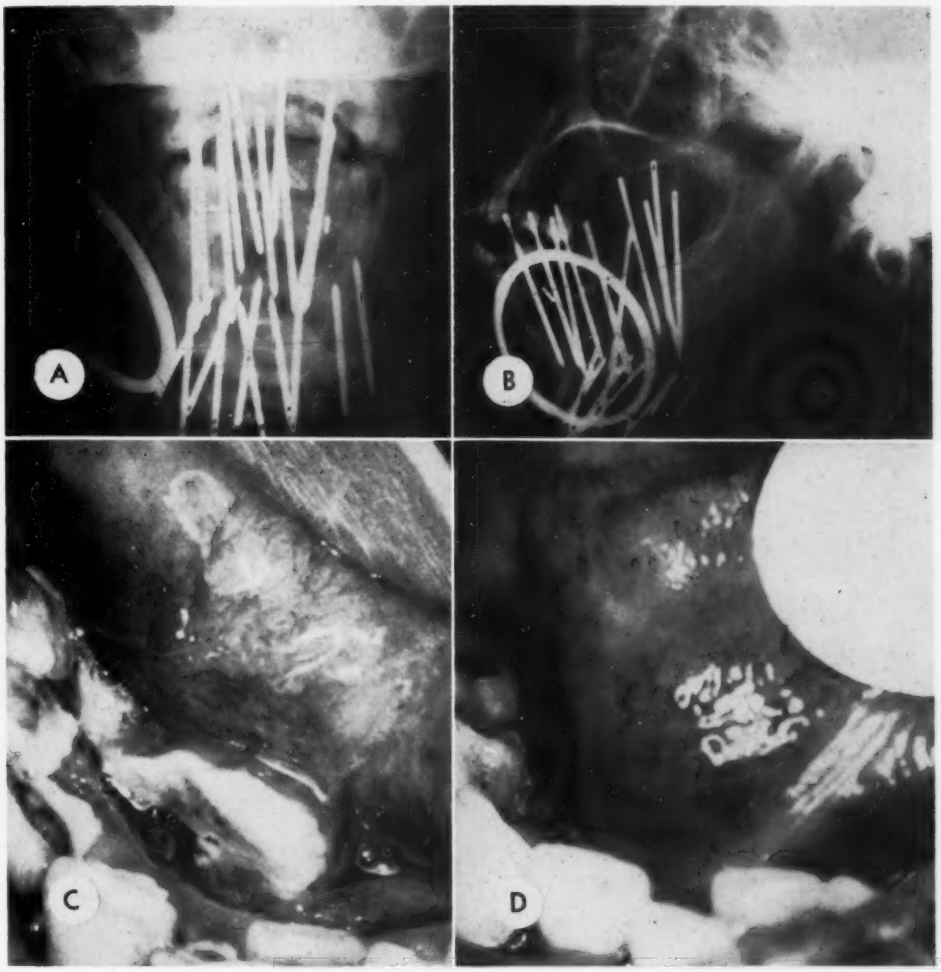


Fig. 4. B.A. 46 N F. *Squamous cell carcinoma of the floor of the mouth, with marked infiltration toward the root of the tongue and the submental region.* The lesion invaded the periosteum but there was no evidence of bone destruction.

(*A* and *B*) Due to attachment to the bone a combined approach was elected. A tumor dose of 3,000 r in 2 weeks was delivered by telecobalt therapy and then radium implantation was performed. It consisted of an intraoral volume and a submental horse-shoe double plane implant as shown in Figure 1*b*. A dose of 3,500 r in 60 hours was delivered by the implants.

(*C*) Lesion before treatment. (*D*) The lesion in the mouth remained controlled, but the patient died after 2 years with uncontrolled supraclavicular metastases.

of all forms of radiation therapy.

Except for the better tolerance by the skin and bone, the foregoing limitations are no less valid when supervoltage therapy is employed.

In order to reduce the total volume of irradiation and to avoid the inclusion of sensitive structures, interstitial radium may be used. In many of these cases a radium implantation can be devised which will properly irradiate the primary lesion and the metastases in the neck, if present, delivering a very small dose to the larynx, pharynx, or spinal cord. In cases where it is doubtful that the radium implant is satisfactory at the beginning of therapy, another alternative may be considered: a combination of external irradiation (conventional or supervoltage) and radium implantation.

Interstitial radium therapy has an important area of application in the treatment of postoperative recurrences of head and neck tumors, most of which arise in a poor

tumor bed with a disturbed blood supply surrounded by considerable scar-like fibrous tissue. Because of this, they are more resistant to irradiation. They require a higher dose and the technique of treatment is generally more difficult, particularly since the tissues have a poor tolerance to irradiation. Interstitial radium therapy is preferable in most of these cases since the dose can be raised to higher levels without danger of producing permanent damage in the normal tissues.

In the treatment of advanced tumors of the head and neck with any technique, radium alone or combined with external beam therapy, it is always advisable to deliver a higher dose where the mass of the tumor is larger and a lower dose to the less voluminous peripheral extensions of the tumor. This is in agreement with two general principles of irradiation of cancer, originated at the Fondation Curie (Paris) and stressed by Fletcher in this country. They are: (1) the central portion (the older part) of the tumor is more resistant to irradiation than the periphery (the growing, younger part) and (2) the sensitivity of any tumor is in inverse ratio to its size.

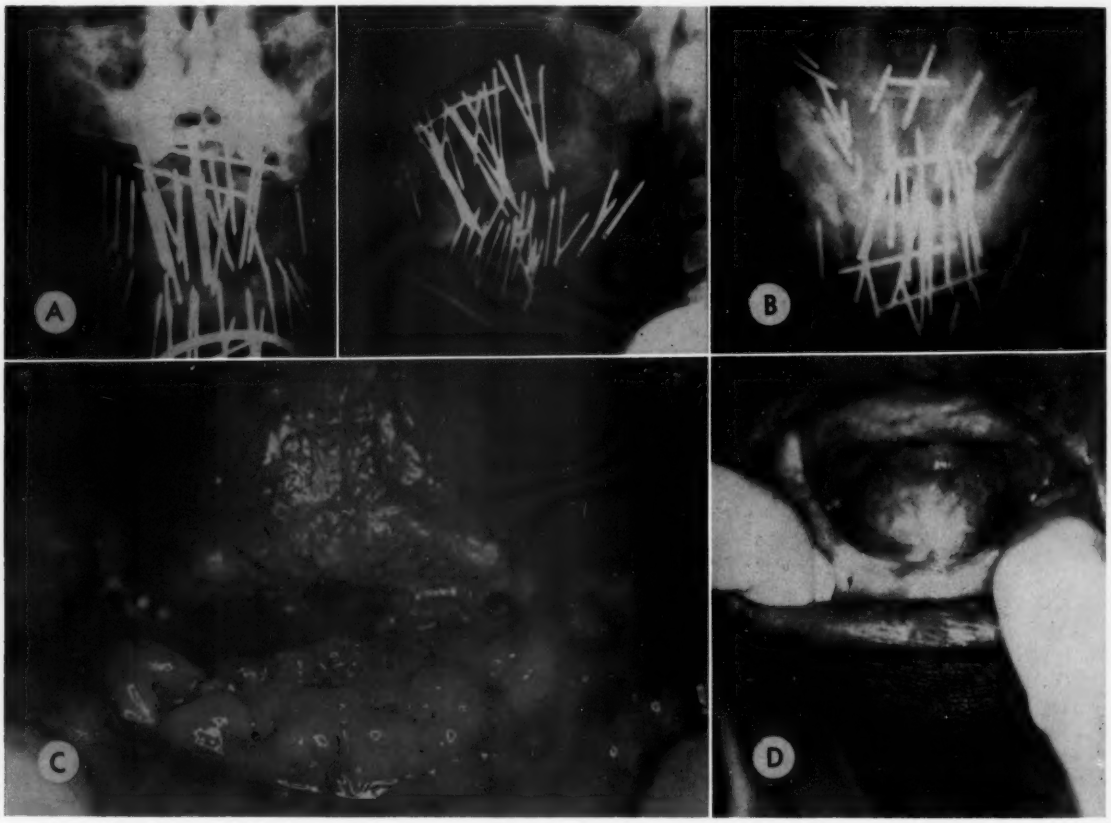


Fig. 5. L. B. 59 N M. *Extensive infiltrating squamous cell carcinoma of the floor of the mouth.* There was involvement of the root and anterior two-thirds of the tongue which was almost completely replaced by tumor; the lower gum was extensively involved and there was questionable bone invasion. Several small hard lymph nodes were palpable in both the submaxillary and the submental regions.

(*A* and *B*) Radium implants of a complex pattern were used, composed of 2 volume plus a palisade curved plane implant for the primary lesion and a single plane implant of full-intensity needles for both submaxillary areas. Both carotid chain areas of the neck were treated "prophylactically" by telecobalt therapy. The dose was 6,500 r in 103 hours for the primary lesion and its extensions; 6,000 r in 99 hours for the submental implant; and 7,000 r in 60 hours at 0.5 cm. for each submaxillary plane.

(*C*) Lesion before treatment. The irradiation and its reaction were very well tolerated by the patient. He had a residual ulceration in the area of the frenulum which took almost a year to heal. (*D*) The patient is free of disease after 2 years. The radiation changes in the tissues are minimal.

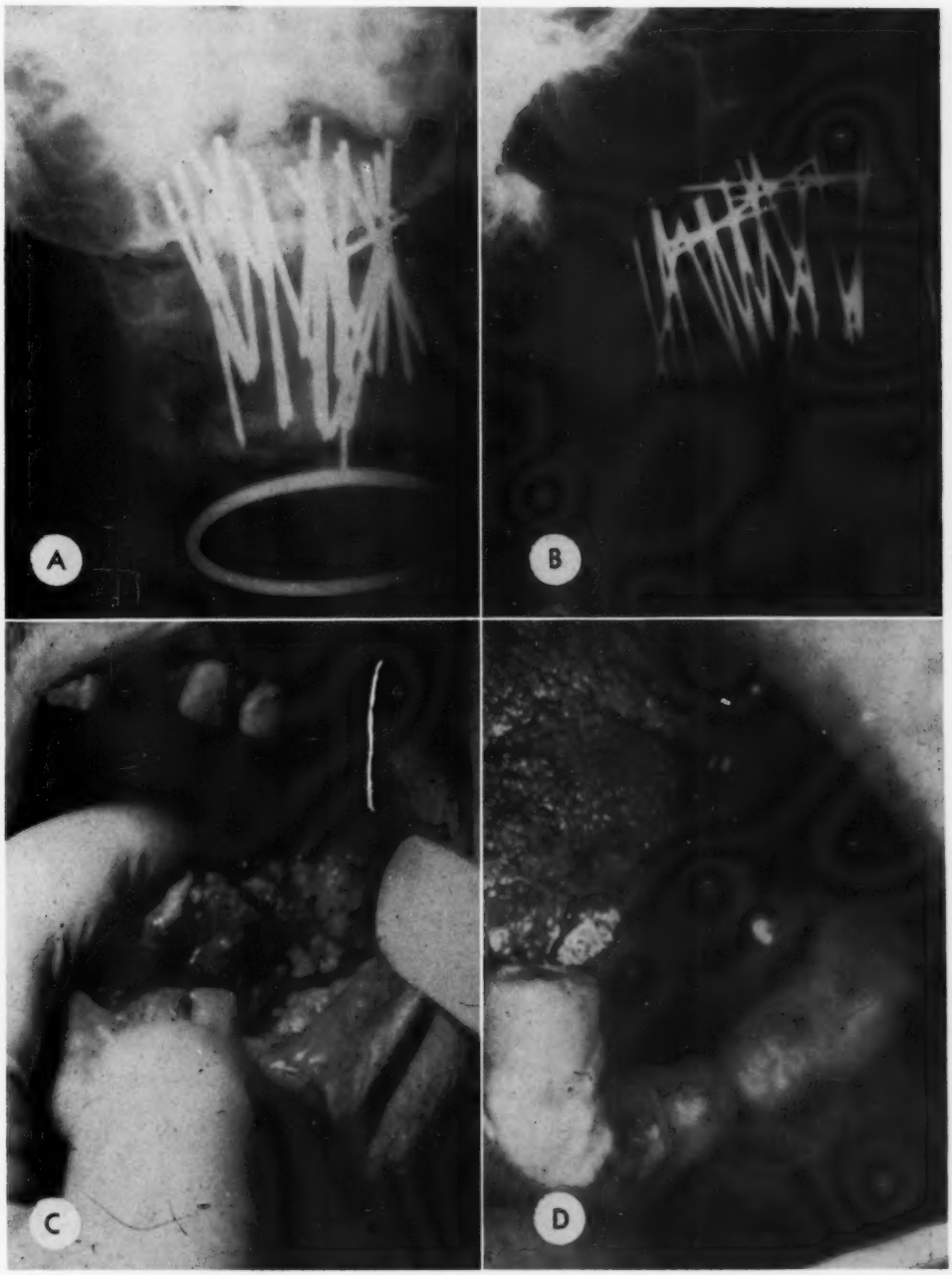


Fig. 6. C.H.P. 57 W M. *Extensive squamous cell carcinoma involving the whole of the tongue (anterior two-thirds and base) and the entire left side of the floor of the mouth.* The patient had several bilateral hard neck lymph nodes and was in a very poor general condition. It was decided to treat the primary lesion by interstitial radium implantation and the neck by telecobalt therapy.

(*A* and *B*) An extensive volume implant was used including the whole tongue and the left floor of the mouth. The implant was satisfactory but due to the extensive necrosis present in the tumor, some of the needles were frequently dislodged. It was, therefore, decided to remove the implant after 4,200 r had been delivered in 66 hours and to complete the treatment with telecobalt therapy, 3,000 r in 2½ weeks. Both sides of the neck received 5,500 r tumor dose in 4 weeks.

(*C*) Lesion before treatment. (*D*) The primary tumor regressed, but there was always a small indurated ulceration on the left side of the tongue with residual tumor which enlarged terminally. The patient died in 6 months with uncontrolled neck metastases (in the irradiated area). The failure to control both the primary lesion and lymph node metastases could be due to the very poor general condition of the patient and the advanced stage of the disease. A higher dose would not have achieved a better result in this case.

It is not uncommon in head and neck tumors to have recurrences, regional metastases and even development of consecutive primary lesions after the original therapy has been completed. As long as the lesion appears to be localized to the head and neck, the patient should not be abandoned, particularly if the primary lesion has been under control for several months or years. The ability to treat near or even within a previously irradiated area by the use of an implant may allow a life to be prolonged with comfort, occasionally for a matter of years.

TECHNIQUE

For the treatment of early lesions the Paterson-Parker system of radium distribution and calculation is the one which best serves the clinical requirements. However, the Paterson-Parker system provides only for the use of a single geometric pattern of radium arrangement, *i.e.*, single plane, double plane and volume implants. It does not provide for complex combinations of single patterns. The other system still in use is the empirical procedure of placing the radium needles in parallel pattern, 1 cm. apart, in a plane or volume, having all the needles of the same intensity. The dose delivered by the latter system is difficult to calculate with clinical accuracy in extensive implants. Without adequate dosimetry it is impossible to predict either the reaction of the normal tissue or the sterilization of the tumor. The extensive radium implantation necessary for the treatment of advanced lesions of the head and neck can be performed with success providing a definite

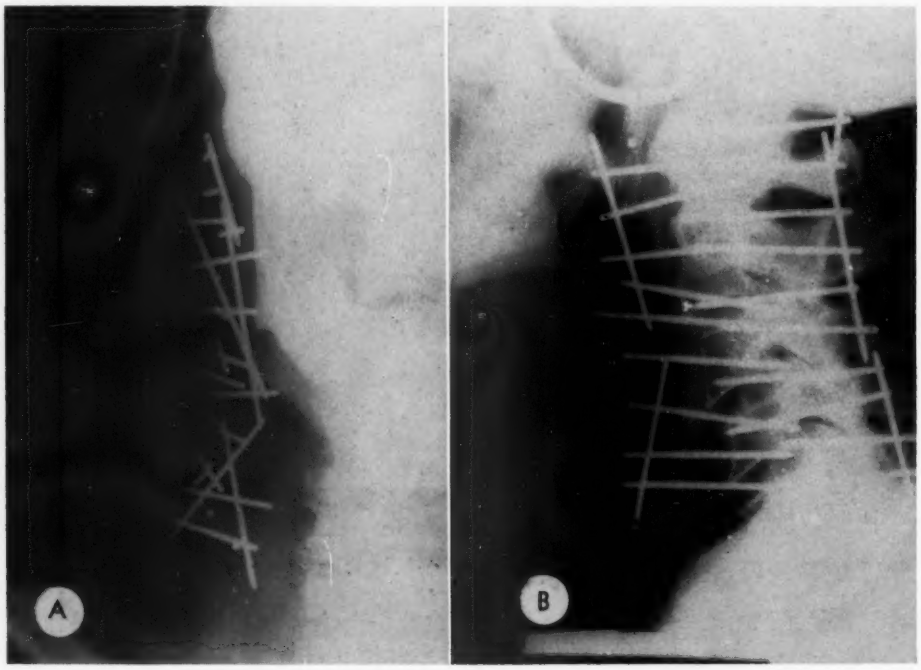


Fig. 7. L.B. 65 W M. *Carcinoma, cylindromatous pattern, involving the right side of the neck in the upper carotid region from the tail of the parotid gland.* The patient came for therapy after a local excision of the tumor mass was performed. It was decided to use combined 220 kv. roentgen therapy and radium implantation, starting with single field external beam therapy.

(*A* and *B*) The implant covered the same area as the field of external irradiation and consisted of a fully crossed single plane application. The patient was lean with a very thin layer of tissue between the carotid and the skin, and a single plane was considered adequate. The dosage was as follows: external beam therapy: upper neck—4,000 r tumor dose in 4 weeks; lower neck—3,000 r tumor dose in 4 weeks; radium implant: 4,000 r at 0.5 cm. from the plane in 73 hours. The reaction was mild.

The patient expired due to intercurrent disease 16 months after therapy without evidence of active disease in the neck. The radiation changes were minimal.

FIG. 8. R.B. 60 W M. *Squamous cell carcinoma, deeply infiltrating, of the right undersurface of the tongue with bilateral extension into the root of the tongue and floor of the mouth.* A deep ulceration almost severed the tongue from its roots (a poor prognostic sign in our experience). Three lymph nodes on the right side of the neck were palpable; the largest 5 cm. in diameter, was proved positive by biopsy.

(*A*) Sketch of extent of the lesion. It was decided to use combined telecobalt therapy and radium implantation. The treatment was started with telecobalt therapy to both the primary tumor and the right side of the neck. After the third week the patient developed repeated copious hemorrhages from the ulceration (lingual artery involvement?) which required ligation of the external carotid artery. This delayed the treatment for one week.

(*B* and *C*) The radium application consisted of a volume implant including the tongue and both sides of the floor of the mouth, and a double plane implant, of half-intensity needles, without crossing, for the residual disease in the right neck. The dosage was as follows: telecobalt therapy: 5,000 r tumor dose in 6 weeks to both the primary lesion and the neck; radium implant: 2,000 r in 35 hours for the primary lesion and 2,500 r minimum in 35 hours for the lymph nodes.

(*D*) Swelling of the neck, due to metastatic lymph nodes before treatment. (*E*) The metastatic lymph nodes of the neck disappeared after treatment, leaving some indurated edema. The primary lesion also regressed, but a flat ulceration remained on the right floor of the mouth from which a positive biopsy was obtained months after therapy.

system is followed in the radium distribution and in the arrangement of sources in geometric patterns. If the needles with proper loading of radium are placed in a definite geometric pattern, the dose delivered in each case is calculable with clinically useful accuracy.

The majority of radium implantations necessary for the treatment of the lesions under discussion call for the combination of

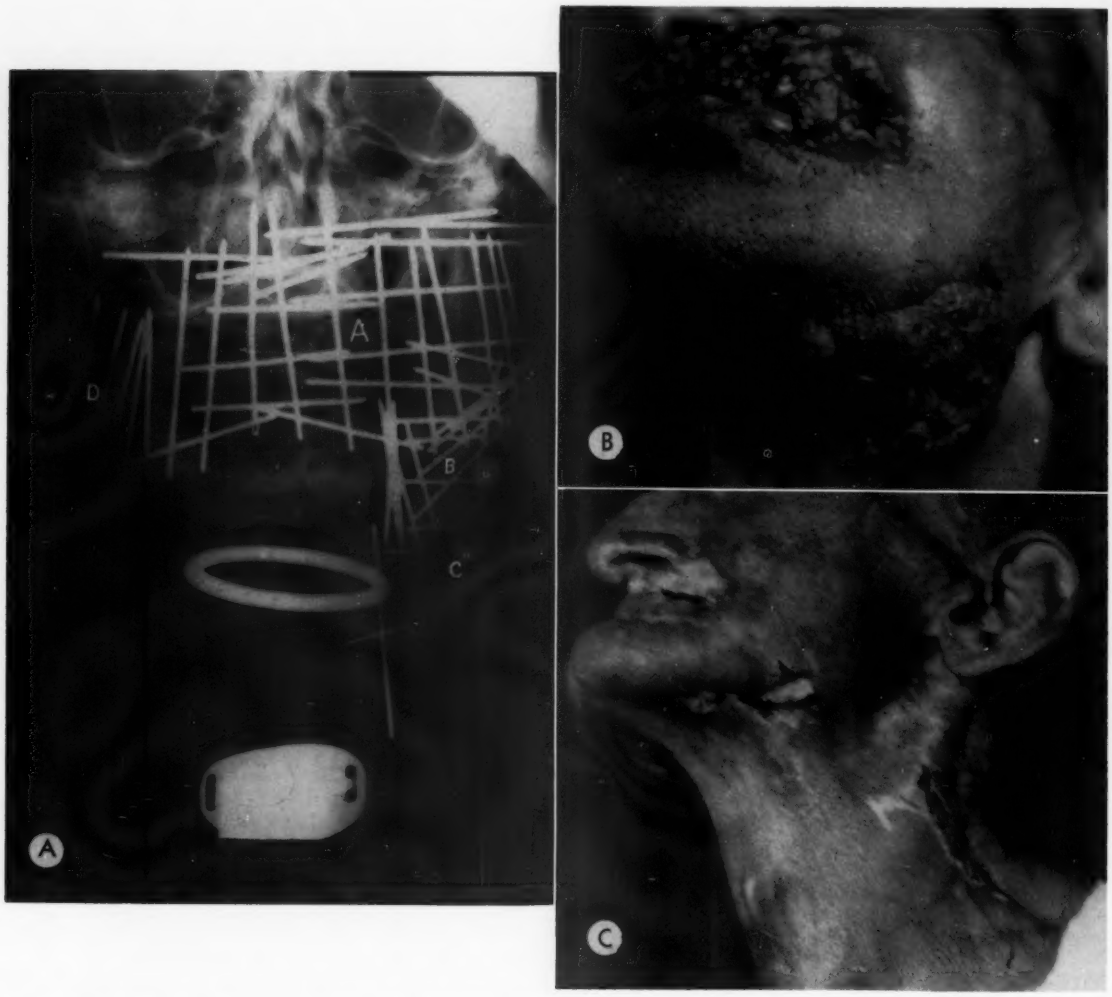


Fig. 9. J.W.S. 66 N M. *Squamous cell carcinoma of the left commissure of the lip with marked extension into the buccal mucosa, whole upper lip and portions of the lower lip and left cheek.* Large ulcerated lymph node metastases (6 cm. in diameter) were present in the left submaxillary region, and two other hard lymph nodes (2 cm. in diameter) were palpable in the upper carotid area. The right buccal mucosa was replaced by a verrucous type of leukoplakia and carcinoma *in situ*. The patient was in a very poor general condition. Only interstitial radium was used.

(*A*) A complex pattern implantation was performed by three consecutive teams of operators. The main features of the pattern were: 2 planes for the primary lesion (A), 3 planes in a triangular arrangement for the submaxillary lymph nodes (B), a single plane of dumbbell needles for the right buccal mucosa (D), and a single plane for the lymph nodes in the left upper carotid area (C). The doses delivered were: 6,000 r in 86 hours for the primary lesion; 8,000 r in 80 hours for the submaxillary lymph nodes; 9,000 r at 0.5 cm. in 92 hours for the upper neck plane; and 6,000 r at 0.5 cm. in 157 hours for the plane in the right buccal mucosa.

(*B*) Extent of lesion before treatment. (*C*) The patient tolerated the treatment very well and the improvement was immediate.

*Comment.* When the bulk of the tumor is large and most of the implant is held within it, the tolerated dose can be very high. Bulky tumors of the squamous cell type, especially in neck metastases, require very high doses of irradiation if control is to be achieved.

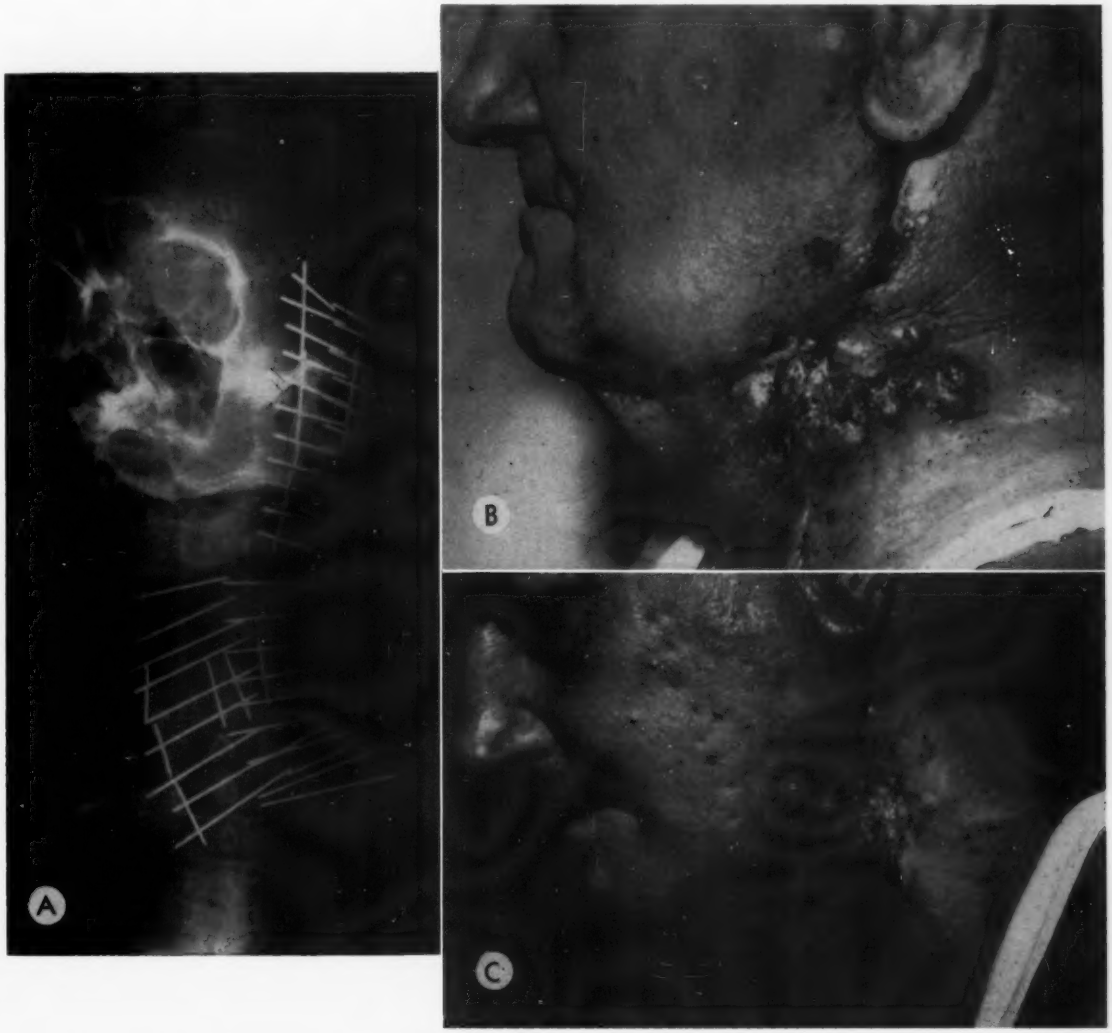


Fig. 10. C.B. 58 W M. *Squamous cell carcinoma of the left side of the neck with left preauricular lymph node metastases, recurrent after radical neck dissection.* The primary lesion in the buccal mucosa, previously treated by irradiation (conventional roentgen rays and interstitial radium), was under control. The disease infiltrated the whole left side of the neck from mastoid to clavicle. Only interstitial radium implantation was performed.

(*A*) A complex pattern radium implant was employed covering satisfactorily the whole of the gross detectable disease except for the posterior portion of the supraclavicular area where treatment was complemented by external beam therapy. The implant was of a parotid plus whole neck type, making use geometrically of a combination of single and double planes. A dose of 9,000 r in 190 hours was delivered to the area where the tumor was bulkiest, and 7,000 r in 68 hours to the rest of the implanted area. The supraclavicular region received 4,000 r in 2 weeks with 220 kv.

(*B*) Extent of lesion before treatment. (*C*) Two months later no tumor was detectable clinically, and the patient was back at work. The patient died of distant metastases 10 months later with the treated areas free of disease.

*Comment.* This patient was treated by interstitial therapy as part of a special study. The local control of the disease was remarkable in this and other similar cases. This type of implantation should not be performed as a routine procedure because of the exposure involved unless the organization of the department permits the performance by several teams of operators or, even better, the use of nylon threaded gamma-ray emitters.

two or more geometric patterns of radium arrangement. It is possible in most of the cases to encompass these lesions by a more or less complex type of implant and, providing the geometric pattern is followed, still have control of the dose delivered.

Homogeneity is not always desirable throughout the radium implant. On the

contrary, following the principle mentioned above, it is better in advanced and bulky lesions to deliver a higher dose to the core of the tumor. It is also more advantageous to have radium needles of such linear intensity as to be able to deliver the total dose in five to seven days, to better spare the normal tissues.

It should be remembered that this type of therapy compares in its extent with radical surgical procedures such as the commando operation, glossectomy (partial or total) plus neck dissection, etc. The surgical procedures are always previously planned; definite steps are followed during their performance as well as during the postoperative period. Radium implantations for any lesion require just as definite a plan if consistent results are to be expected.

Before undertaking this type of therapy, the patient should be put in the best possible physiologic state. Special attention should be paid to the blood volume, hemoglobin and hematocrit, serum protein level, and the fluid and electrolyte balance. The nutrition should be improved, if necessary by way of nasogastric tubes or intravenous fluids and the infections should be treated. In most of the cases the treatment of the neoplasm is not an emergency and by improving the general condition of the patient, the effectiveness of the irradiation is enhanced. In many cases ancillary procedures such as tracheostomy, the extraction of decayed teeth, etc., are necessary.

The care of patients while the implant is in place is also important. No less important is the care thereafter; pain relief, oral hygiene, and proper feeding may mean the difference between success and failure.

In most of the cases in this group, the type of implant required is of the complex pattern variety. Such implants are tailored to the disease and its extensions by using a combination of single patterns: volume and planar. Any single component can be repeated as often as required, providing no undesired hot or cold spots are formed. The usual rules of radium distribution for single patterns must be altered in some complex implants as the case requires, *i.e.*, the end of the plane close to another implant should not be crossed if a hot spot is to be avoided; some implantations are performed either with full or half intensity needles in order to obtain a more suitable isodose.

## DOSAGE

The general scheme of dose-time relationship already mentioned is followed. In very extensive implants the dose delivered is highest at the site where the tumor is bulkier and lowest in the areas where the tumor is not clinically demonstrable, but which are potentially involved by microscopic extensions. This variation in the dose delivered is achieved by taking advantage of the different loadings of the needles and by removing parts of the implant at different times. Each component part of an implant is calculated separately and its contribution to the other parts considered. It is very useful to thread needles of different loadings with different colored threads, and it will help in the calculation of the different portions of the implant to have a detailed sketch of the needles made simultaneously with the implantation.

## SUMMARY

1. Advanced squamous cell carcinomas of the head and neck, even with neck metastases, are tumors which remain localized above the clavicle for relatively long periods of time.

2. In all cases radical therapy should be the treatment of choice even if in many cases the result will be palliation only. With this policy more cures and better palliation can be obtained.

3. In this group of patients interstitial treatment should be performed whenever possible because of the reduced irradiation of normal tissues and the enhanced probability of cure due to the previously mentioned advantages.

4. Postoperative residual or recurrent tumors are often best treated by interstitial gamma-ray therapy.

5. Careful preoperative care, planning and performance of the implant and postoperative care are of paramount importance in obtaining the best results.

6. Careful follow-up with adequate treatment of new tumor foci as they appear will allow long survival free of symptoms, in many cases of advanced tumors of the head and neck even where a cure is not obtained.

7. Extensive interstitial treatment is possible in the head and neck lesions and encouraging results can be obtained when the proper indications and techniques are followed.

## PART III. COMBINED EXTERNAL BEAM IRRADIATION AND INTERSTITIAL THERAPY IN HEAD AND NECK TUMORS

### GENERAL CONSIDERATIONS

Based upon the general principles already discussed, efforts were made to reduce the volume of heavy irradiation, particularly the unnecessary irradiation of normal tissues, in the treatment of head and neck tumors whenever possible. This became more important with the increasing use of supervoltage therapy since this modality, in general, does not reduce the volume of normal tissue irradiated. On the contrary, with the increased depth dose characteristic of this type of therapy and the popular use of two parallel-opposing fields, the volume of heavy irradiation, in most cases, extends from side to side of the face and/or neck with inclusion of much normal tissue, as well as the tumor, between the fields. The dose delivered by such a technique is sometimes higher in tissues outside the tumor bearing area than in the tumor itself (Fig. 11).

In search of a better tecnhical arrangement to deliver a lethal dose to a tumor bearing area when only conventional therapy of 1 mm. Cu half value layer was available to us, we began to study the possibilities of the combined technique of external beam irradiation and interstitial therapy. When cobalt 60 teletherapy in combination with interstitial treatment was investigated, it became obvious that such an approach had the same advantage of reducing the volume of high irradiation with the additional benefits intrinsic to supervoltage therapy (Fig. 11). Perhaps, by the use of a short-distance cobalt or cesium unit combined with a radium implant, the maximum benefits of this technique might be obtained—the further reduction of the volume of high irradiation together with the advantages of supervoltage external beam therapy.

The dosimetry of the combined technique is illustrated in Figure 12.

The concept of combining external beam and interstitial therapy is not a novel one in treating head and neck tumors. Indeed, several schools of radiation therapy have been using it for years (McWhirter, Fletcher, Martin, and others) and found it to be of definite value.

### PRINCIPAL MODES OF COMBINATION

We have used the following principal modes of this combination:

GROUP 1. *Interstitial gamma therapy as a complement of external beam therapy.* Here, the fundamental part of the treatment is the external beam irradiation. In these cases the dose to the normal tissues is close to the tolerance level, but, at the end of treatment, there still remains a considerable amount of residual tumor at the site of the primary lesion and/or in the neck lymph nodes. This indication is related to the principle mentioned before of delivering higher doses to the bulkier portion of the tumor (see Part II).

This procedure is of greatest value in cases of well-differentiated carcinomas, particularly those of the floor of the mouth, base of the tongue or retromolar trigone, in some tonsillar and peritonsillar tumors, and with large lymph node metastases in the neck. In all cases an effort is made to keep the implant within the residual tumor itself in order to further spare the normal tissues (Fig. 13, 14 and 15).

GROUP 2. *External beam therapy as a complement of interstitial radium therapy.* This

method is used in cases where the important part of the treatment is the radium implantation, and the external irradiation is added as a complement. These cases can be subdivided into two categories:

(a) External irradiation before the interstitial irradiation. This type of therapy is indicated in the cases where interstitial irradiation is the treatment of choice but where complete coverage of the tumor by an implant cannot be assured, either because of its extension or anatomic location. The external irradiation is intended to reduce the extent and the volume of the tumor in order to ensure that the whole tumor bearing volume can be properly covered by the implant. The main indications are large lesions of the floor of the mouth with extension close to, or involving bone; extensive buccal mucosal lesions involving the pterygoid region, the anterior pillar, or lower or upper gum; postoperative recurrences of parotid tumors or neck metastases, and very extensive lesions of the tongue with invasion of the floor of the mouth close to or invading the lower gum (Fig. 16, 17 and 18).

(b) External irradiation after the interstitial radium. This sequence is followed in cases where roentgenograms show that the pattern of the implant is not completely satisfactory, with either questionable cov-

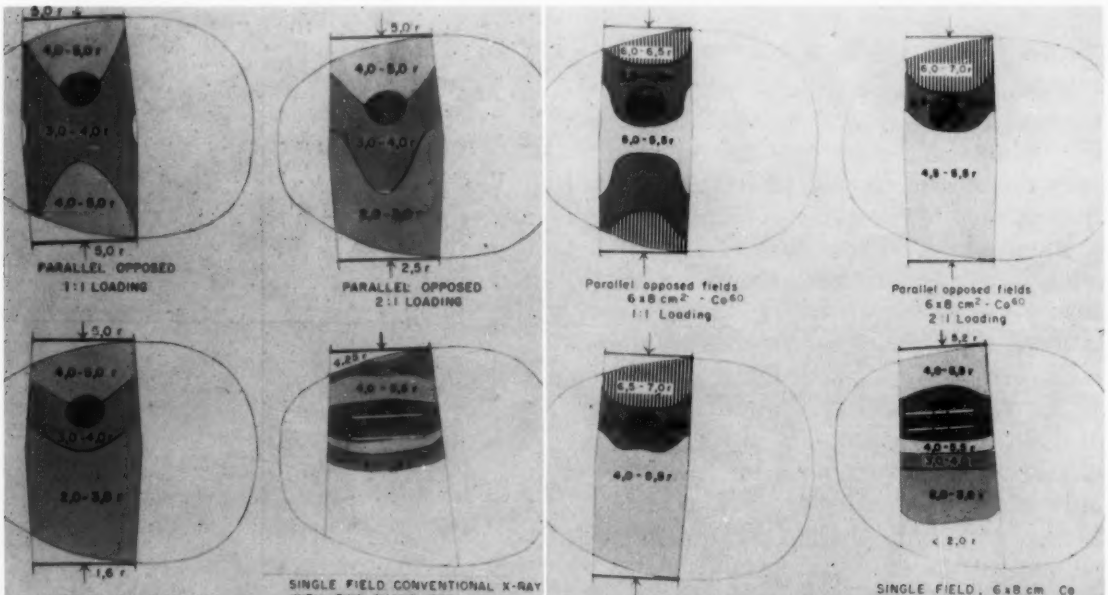


FIG. 11. These figures show the different volumes of heavy irradiation (above 5,000 r) with the varied techniques commonly used for a tonsillar tumor.

(*A*) *Technique with conventional roentgen rays* (220 kv., 1 mm. Cu half value layer). With conventional roentgen therapy and a 2 parallel-opposing field arrangement, it is very difficult to obtain a lethal dose for squamous cell carcinoma unless the tolerance of the normal tissue is exceeded. Differential loading will improve the distribution of dose and will diminish the unnecessary heavy irradiation of normal tissues. Single field external beam combined with interstitial radium is the best arrangement for delivery of the proper dose to the desired site with a minimum of irradiation of the normal tissues.

(*B*) *Technique with telecobalt* (50 cm. distance). The above comments also apply here. The volume of heavy irradiation is larger than for 220 kv. roentgen rays. The advantages of differential loading are not as important as with conventional beam therapy. Again the best arrangement of dose distribution is with external cobalt beam and interstitial radium. The radium implant does not have to be of a double plane pattern. In most of the cases a single plane will build up the dose from within satisfactorily. For most tumors situated laterally, the best technique of treatment would probably be achieved by using short-distance cobalt or cesium external beam therapy and a radium implant.

erage of the whole lesion or lack of uniform dosage (Fig. 19), and where the radium needles have not maintained their position during treatment, or when one or several needles have become dislodged from their proper places, necessitating premature removal of the implant (Fig. 20).

GROUP 3. *External beam therapy and interstitial therapy equally important.* In the techniques already described, implantation procedures are planned and executed with the intent to encompass the entire lesion. In this group of cases such coverage is not necessary. The implantation of radioactive sources is planned and executed so as to provide an internal field of irradiation. The aim is to produce between the external irradiation field and the "interstitial field" a proper volume of high dose irradiation which will adequately cover the tumor bearing tissues. This can usually be achieved by a single plane implant, although sometimes a double plane implant is required. It is not necessary to "cover" the whole tumor in the transverse diameter because the irradiation of the outer portion of the tumor volume is provided mainly by the external beam.

Here, the combination technique is used as an *established technique of choice and both external and interstitial irradiation are equally important* in the management of the lesion. In this group of patients the lesion is treated by an external field of irradiation (external beam roentgen rays or cobalt 60 teletherapy) and the "internal field" created by the radium implant. This technique makes full use of all the advantages of the combined procedure (Fig. 11). It is especially indicated for lesions involving laterally placed structures. The main indications are: some large tumors of the buccal mucosa, lesions of the buccinator region, retromolar trigone, some lesions of the lateral portion of the floor of the mouth, especially with extension into the lower gum, lesions of the gums, lesions of both upper and lower buccal gingival sulci, some lesions of the tonsil and peritonsillar regions (palatoglossal and glossotonsillar sulcus), some large metastases in the neck, and large inoperable lesions of the parotid gland (Fig. 21, 22 and 23).

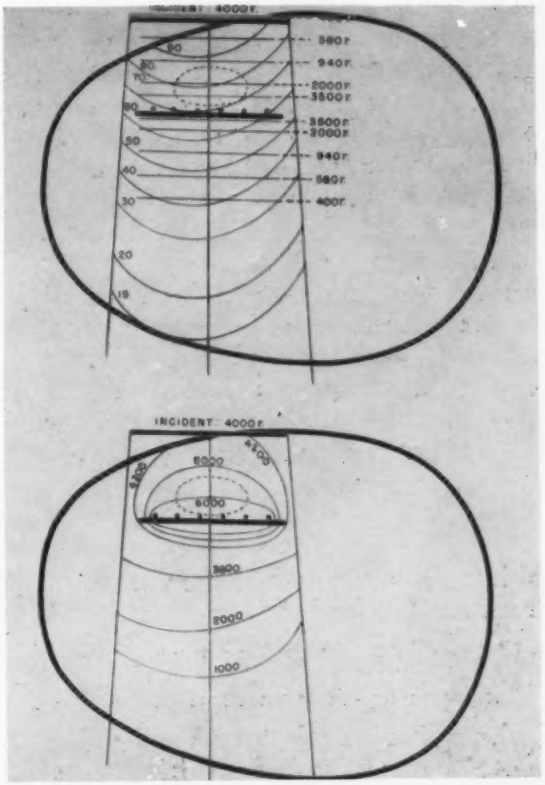


FIG. 12. *Dosimetry.* In all cases where a combined technique is employed, the dose is calculated as indicated in this sketch by observing the following steps: (1) an accurate contour of the patient is drawn at the proper level; (2) the isodose curves of the single field of external irradiation are marked in, allowing for the inverse square law correction; (3) an accurate localization of the lesion and radium implant is made with respect to the contour by direct measurement on the patient and roentgenographic films; (4) the output of the implant every 0.5 cm. is superimposed on the isodose curves from the external beam; (5) at every intersection of two lines, the doses are added and a combined isodose curve is made showing the total contribution from both sources.

We are aware that the addition of the conventional 220 kv. to gamma radiation is not biologically correct; however, this procedure has been useful in establishing a basis of technique and dosimetry.

## DOSAGE

Whenever possible the dose delivered by the single field is kept well within tolerance of the normal tissues. In cases where conventional energies are used, we try not to exceed 5,000 r skin dose. When super-

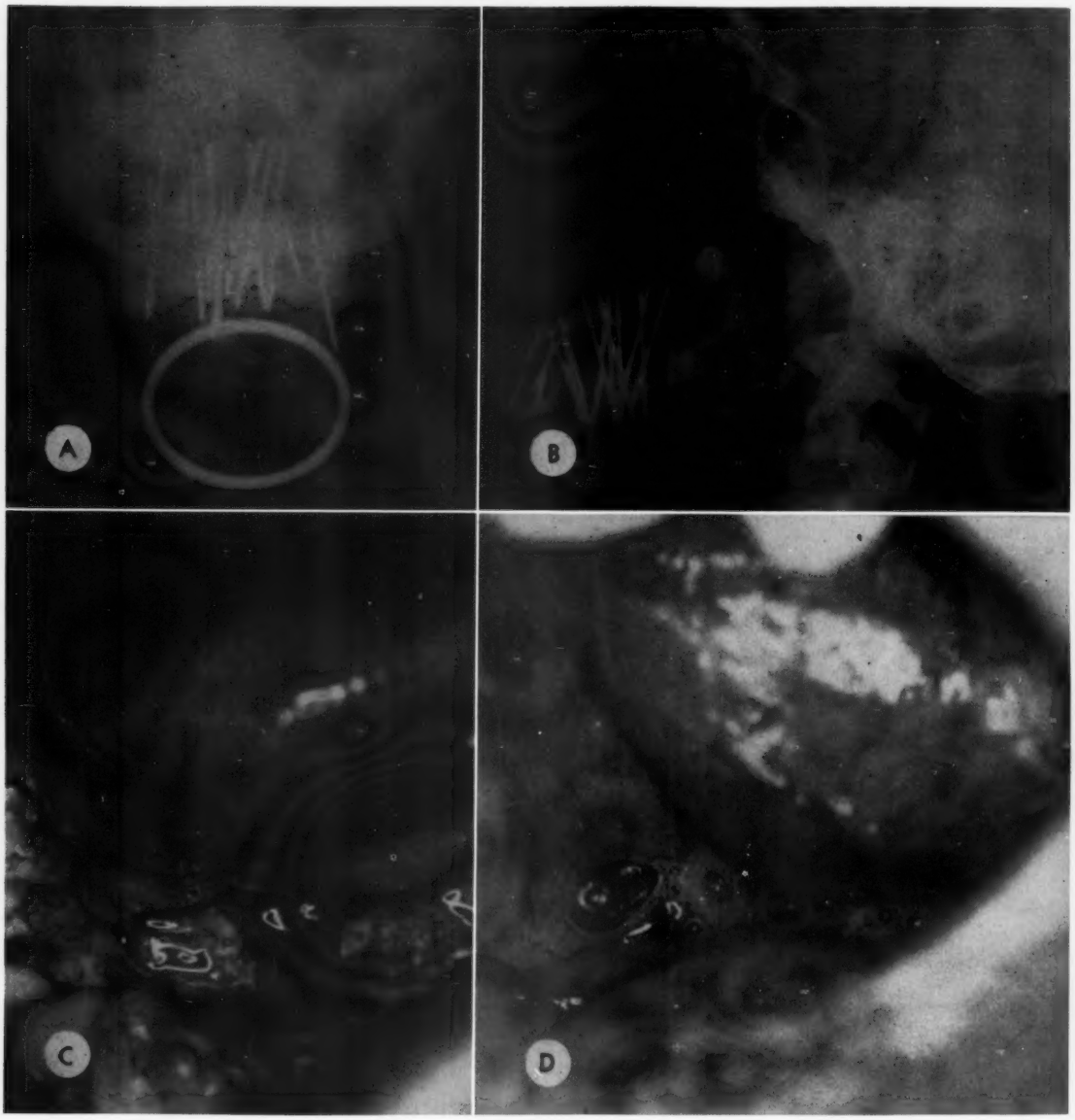


Fig. 13. C.F. 55 W M. *Squamous cell carcinoma of the floor of the mouth, anterior portion, with extension toward both lateral portions.* The gum was involved anteriorly with invasion and exposure of the bone. A submental lymph node, 1.5 cm. in diameter, was palpated. The patient was in a good general condition. Due to the extension of the disease and the amount of bone involvement, it was decided to treat the primary lesion and both lymph node bearing areas with telecobalt after which a radium implant was placed into the residual tumor itself.

(*A* and *B*) The implant consisted of a single volume through the tongue, and extended out to the periosteum anteriorly and laterally. A curved palisade-type of plane was added to cover the area of gum and bone invaded by disease. With telecobalt therapy the primary lesion and upper neck received 5,800 r tumor dose in 5 weeks and both supraclavicular areas and lower neck 5,000 r in 4 weeks. The implant, applied 2 weeks after the external therapy was finished, added 1,000 r in 20 hours.

(*C*) Lesion before treatment. (*D*) The major portion of the lesion regressed one month after therapy. On the floor of the mouth, anteriorly, close to the bone, a small ulceration with an indurated base remained, without symptoms. Ten months later the induration increased and a positive biopsy was obtained from the area. Surgery was performed a year after therapy, and the patient died of septicemia produced by a postoperative infection.

*Comment.* This patient obtained a year of comfortable life from the treatment. There is no doubt that the heavy irradiation contributed to the poor defense shown by the tissues against infection.

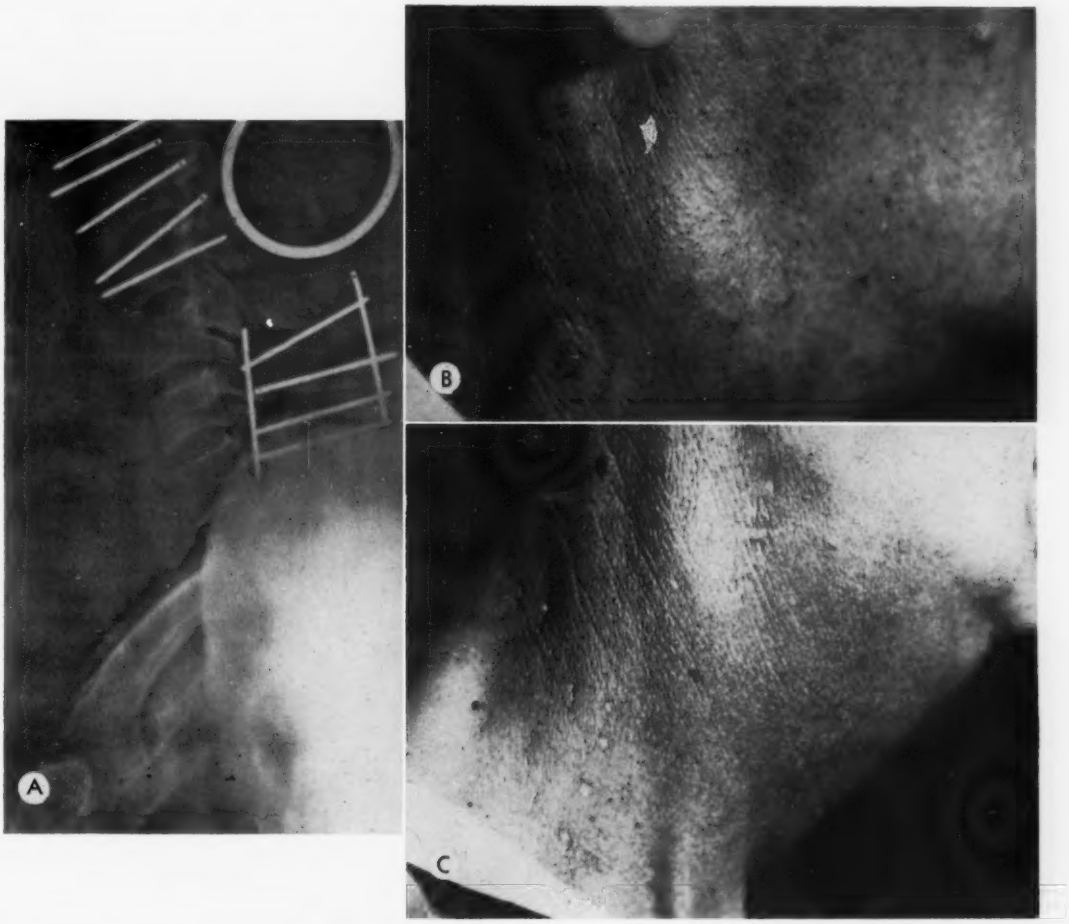


Fig. 14. W.W. 50 W M. *Squamous cell carcinoma of the right pyriform sinus with homolateral neck metastases.* The primary tumor was very extensive and the neck metastases consisted of 3 matted lymph nodes, the largest of which measured 5×7.5 cm. in diameter, situated in the upper portion of the carotid chain. Positive biopsies were obtained from both the primary lesion and the lymph nodes. The patient developed a 1.5 cm. lymph node low in the posterior triangle of the neck during treatment. Telecobalt therapy was used for the primary lesion; combined telecobalt therapy and radium implantation for the lymph nodes. The implantation was performed 2 weeks after completion of the external therapy, to include only the residual, palpable disease in the neck.

(*A*) The upper implantation was done with half-intensity needles; the lower with a typical Paterson-Parker radium arrangement. The dosage was as follows: the primary lesion received 7,000 r tumor dose in 6½ weeks by telecobalt therapy; the metastases in the upper neck received 7,500 r tumor dose in 6½ weeks by telecobalt therapy plus 1,000 r by interstitial radium. The metastases in the lower neck received 5,000 r tumor dose in 4 weeks by telecobalt therapy plus 2,500 r by the radium implantation.

(*B*) Swelling of the neck, due to metastatic lymph nodes, before treatment. (*C*) The lymph nodes in the upper carotid chain regressed completely, leaving some indurated edema of the region. The lymph nodes in the lower neck regressed partially in size to regrow 10 months later at which time a positive biopsy was obtained. A radical neck dissection was performed 1 year after treatment showing no residual disease in the upper carotid chain and a 2×3 cm. positive lymph node low in the posterior triangle of the neck. The incision healed per primam intentionem and the patient is without evidence of disease 18 months after therapy.

*Comment.* For small residual lymph nodes, implants using half-intensity needles are advisable to increase the dose only in the tumor area with minimal dose to the skin and other normal tissues. The sterilization of large masses of lymph node metastases in the neck is possible only by very heavy irradiation. Neck dissection after heavy irradiation is feasible without untoward complications provided the techniques of both irradiation and surgery are proper. The recurrence in the lower neck in this patient was perhaps due to the fact that this lymph node was situated too near the margin of the field of cobalt therapy and thus may have been inadequately irradiated.

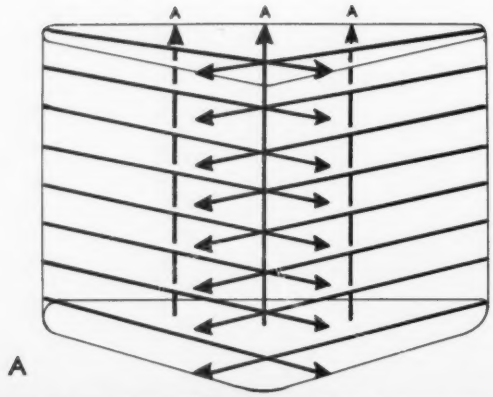

FIG. 15. H.W. 63 W F. *Metastatic squamous cell carcinoma in the lymph nodes of the right upper carotid chain proved by biopsy.* The mass was fixed and measured 5 cm. in its greatest diameter. The primary lesion on the left side of the soft palate was treated by surgical excision 9 months previously and was under control. A combined technique of telecobalt therapy and interstitial radium was used. The telecobalt therapy with anterior and posterior tangential fields included the entire right side of the neck.

(*A*, *B* and *C*) The radium implant consisted of a triangular, 3 plane arrangement of half-intensity needles without crossing. This pattern is best suited for irradiation of large masses in the neck with minimal damage to the skin since the dose is very uniform within the implant. In the present case the dose was 5,000 r tumor dose in 4 weeks by telecobalt therapy and 2,500 r in 55 hours by interstitial radium.

(*D*) Swelling of the neck due to metastatic lymph node involvement before treatment. (*E*) The treatment was very well tolerated. The patient is free of disease 1 year after therapy.

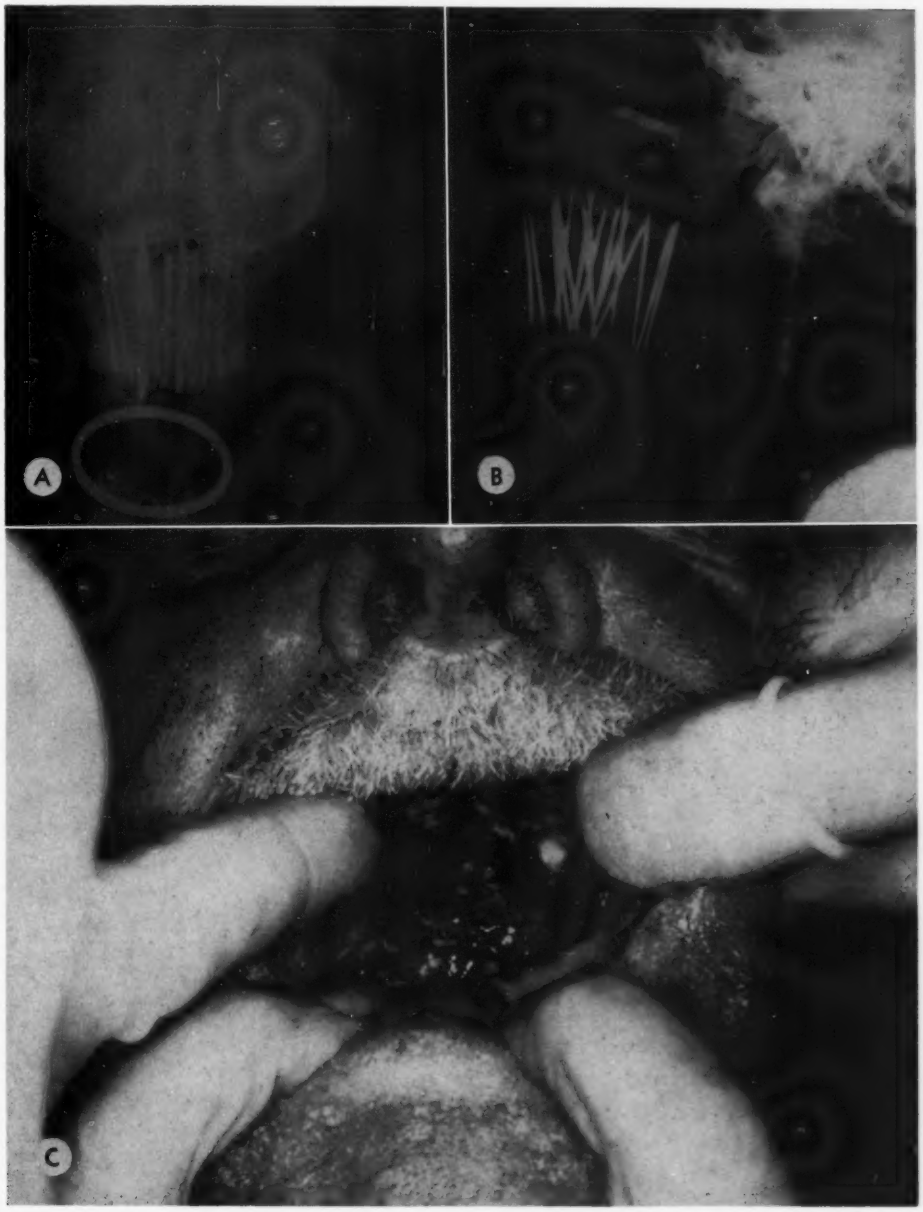


Fig. 16. H.L. 66 W M. *Squamous cell carcinoma involving the whole of the anterior two-thirds of the tongue with invasion of both sides of the floor of the mouth.* The root of the tongue was deeply infiltrated by tumor. No lymph nodes were palpable in the neck. Combined telecobalt therapy and interstitial radium was used rather than implantation alone because of the extent of the disease and its proximity to the bone.

(*A* and *B*) The implant was a simple volume implant which included the whole tongue and floor of the mouth. The dose was 4,000 r tumor dose in 4 weeks by telecobalt therapy and 3,500 r in 54 hours by interstitial radium.

(*C*) Lesion before treatment which was well tolerated. The patient obtained partial regression of the lesion but it started to regrow after 4 months.

*Comment.* In our experience, it has been difficult to obtain even temporary control of this type of massive tumor of the tongue by any radiation technique.

voltage is used, an effort is made to remain at a maximum dose of 6,000 r in the subcutaneous tissues of the entrance field in order to avoid delayed changes with consequent deep fibrosis and sometimes necrosis as have been described in patients treated several years ago with high doses of supervoltage irradiation.

The proportion of the total tumor dose delivered by the external and interstitial irradiation varies with the type of combination used. We have been using the following

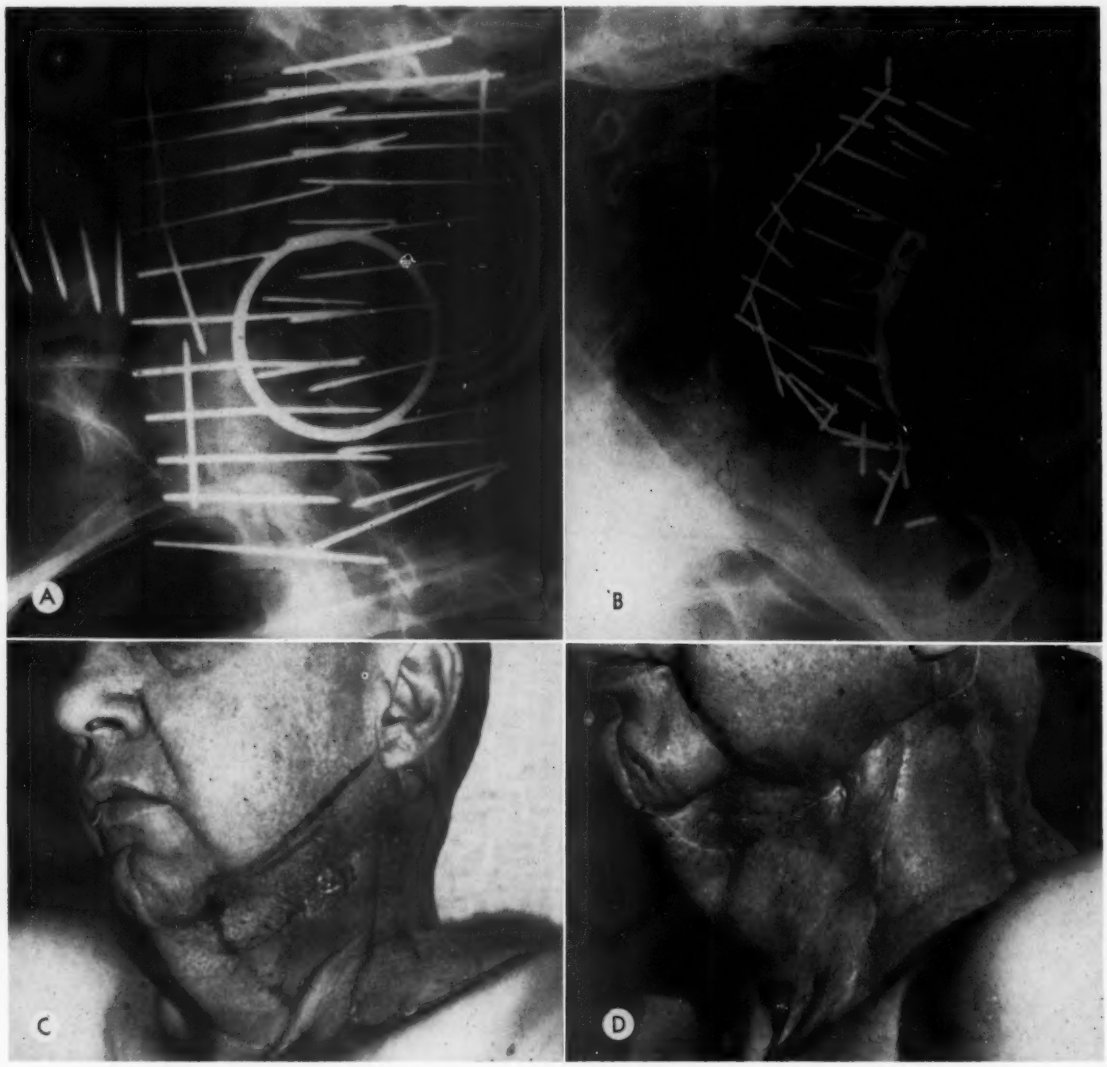


Fig. 17. D.S. 54 W M. *Extensive recurrent squamous cell carcinoma of the left side of the neck.* The primary lesion of the lateral border of the tongue was treated by surgery one year previously and was under control. At the time of the operation a commando procedure was performed with a radical neck dissection. Tumor was known to be left attached to the carotid bulb. The "recurrence" involved the whole left side of the neck with a shell-like subcutaneous infiltration which was not over 1 cm. thick in most of its extensions. It was decided to use a combined procedure of telecobalt therapy and interstitial radium. The telecobalt therapy with a single field covered an area extending from the mastoid to the clavicle.

(*A* and *B*) The interstitial radium application consisted of a single plane implant following the Paterson-Parker rules of distribution. A dose of 3,000 r tumor dose was delivered in 3 weeks by telecobalt therapy. The radium implant delivered 4,000 r in 58 hours and followed the external irradiation without interval.

(*C*) Extent of lesion before treatment. (*D*) The treatment was well tolerated. The local control of the disease was good, and the treated area remained free of disease even though the paitient died 18 months later because of distant metastases.

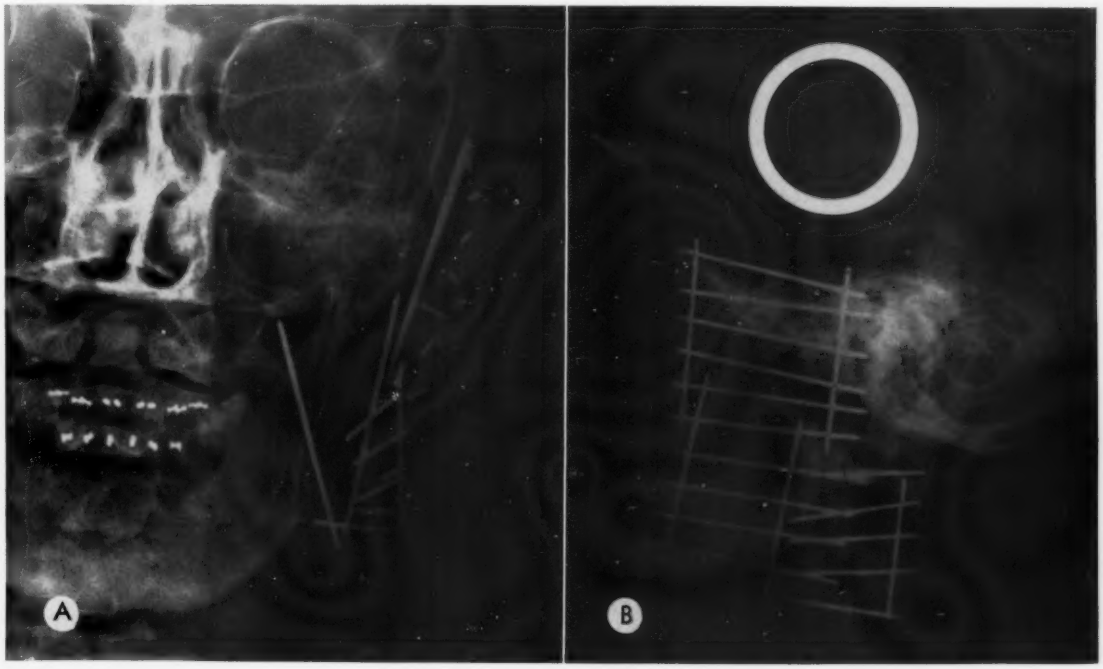


Fig 18. *Parotid implant.* In most cases of inoperable malignant tumors of the parotid gland or postsurgical recurrences, we prefer to use interstitial radium therapy. An exception is made in cases of very large tumors where a proper implant is not feasible at the beginning.

*Treatment.* The implant has been described in a previous paper (F.B.[1]). The extension of the deep portion of the implant is determined by the position of the tumor. The upper neck is included so as to irradiate the lymph nodes most commonly involved (carotid chain). The postoperative implants are performed 2 weeks after the operation (see example below); if performed earlier, there is interference with the wound healing. In most of the postoperative recurrences, the tumor is multiple but of small volume. Thus, a radium implant alone is the treatment of choice. In cases with bulky tumors, a combined approach with telecobalt therapy and interstitial radium is generally indicated.

*Dosage.* For postoperative treatment we try to deliver 6,000 to 7,000 r in 6 to 7 days at 0.5 cm. from each plane. When tumor is present, we deliver from 8,000 to 8,500 r at the site of the tumor and 6,000 to 7,000 r to the rest of the treated area at the same time. If combined therapy is used, 3,000 to 4,000 r will be delivered prior to the implantation in 2 to 3 weeks and the rest, up to the previous doses, by the implant. This has proved to be well tolerated by all the patients, with a minimum of immediate and late radiation reactions and without a resulting "dry mouth."

S.A. 36 W M received postoperative treatment for a malignant mucoepidermoid carcinoma. The original tumor was 3 cm. in diameter, located in the upper portion of the superficial parotid lobe.

(*A* and *B*) The aim of the implantation was to cover mainly the superficial portion of the parotid, and 7,000 r was delivered in 150 hours. The reaction was very slight.

The patient is free of disease 2 years after therapy, showing only slight radiation changes.

ranges of dosage which should be modified according to each particular case:

GROUP 1. Full radical treatment with external irradiation (cobalt teletherapy) followed by 1,000 to 2,000 r delivered by interstitial irradiation to the core of the residual tumor.

GROUP 2. (a) Initially, 2,000–3,000 r tumor dose by external irradiation, or whatever amount is necessary to produce the desired shrinkage of the tumor. The interstitial treatment then delivers the dose necessary to arrive at a total of 6,500 to 7,000 r in all. In very large tumors, an additional 500 to 700 r is delivered to the core of the tumor by leaving in the necessary group of needles the required extra time.

(b) No definite dosage can be assessed in this group as the different proportions depend upon the dose which had been delivered by the radium prior to its removal. However, a total of 6,500 r is seldom to be exceeded as the tolerance of the tissue to a combined procedure is less than when radium is used alone, due to the increased volume of tissue being irradiated.

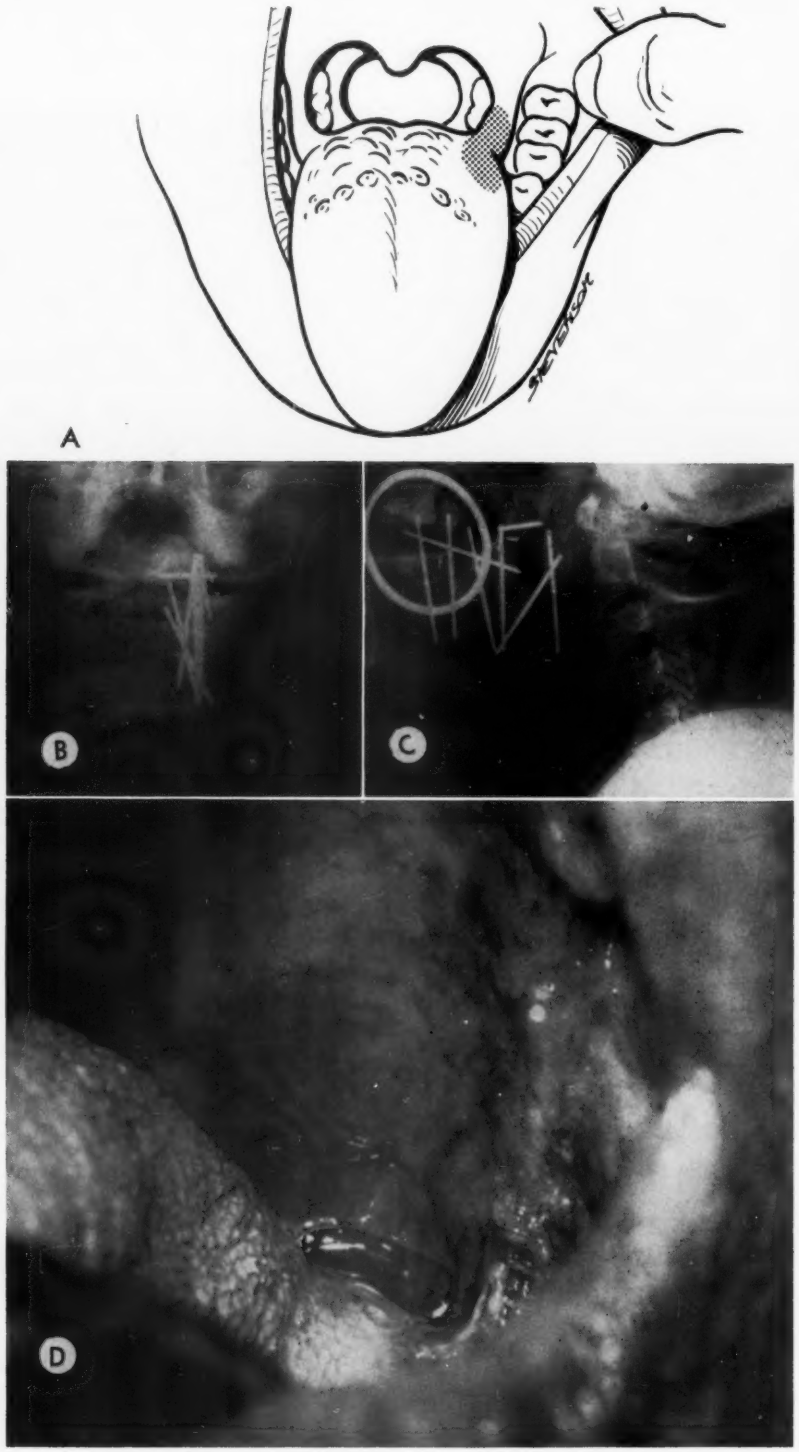


FIG. 19. L.F. 57 N F. *Squamous cell carcinoma of the palatoglossal fold with a small extension into the tongue.* No lymph nodes were palpable in the neck.

(*A*) Sketch of the lesion. It was decided to treat this lesion with interstitial radium alone.

(*B* and *C*) An implant of the single plane type was used in the most posterior portion of the lateral aspect of the tongue with one additional needle in each faucial pillar (anterior and posterior). The crossing needles were inserted in the tongue and in the soft palate. Silver clips were placed to mark the position of the lesion in relation to the implant. The roentgenograms taken of the implant showed it to be unsatisfactory as the lesion was covered only by the superior edge of the implant. The radium was removed and treatment was completed by telecobalt using a single small field. The interstitial treatment was useful in raising the dose from the medial aspect. The implant delivered 1,000 r to the lesion and the external irradiation 5,000 r tumor dose in 4 weeks.

(*D*) The reaction was mild. The patient is alive with no evidence of disease 3 years later showing no radiation changes in the mouth.

*Comment.* If an implant is not satisfactory, it should be removed without hesitation.

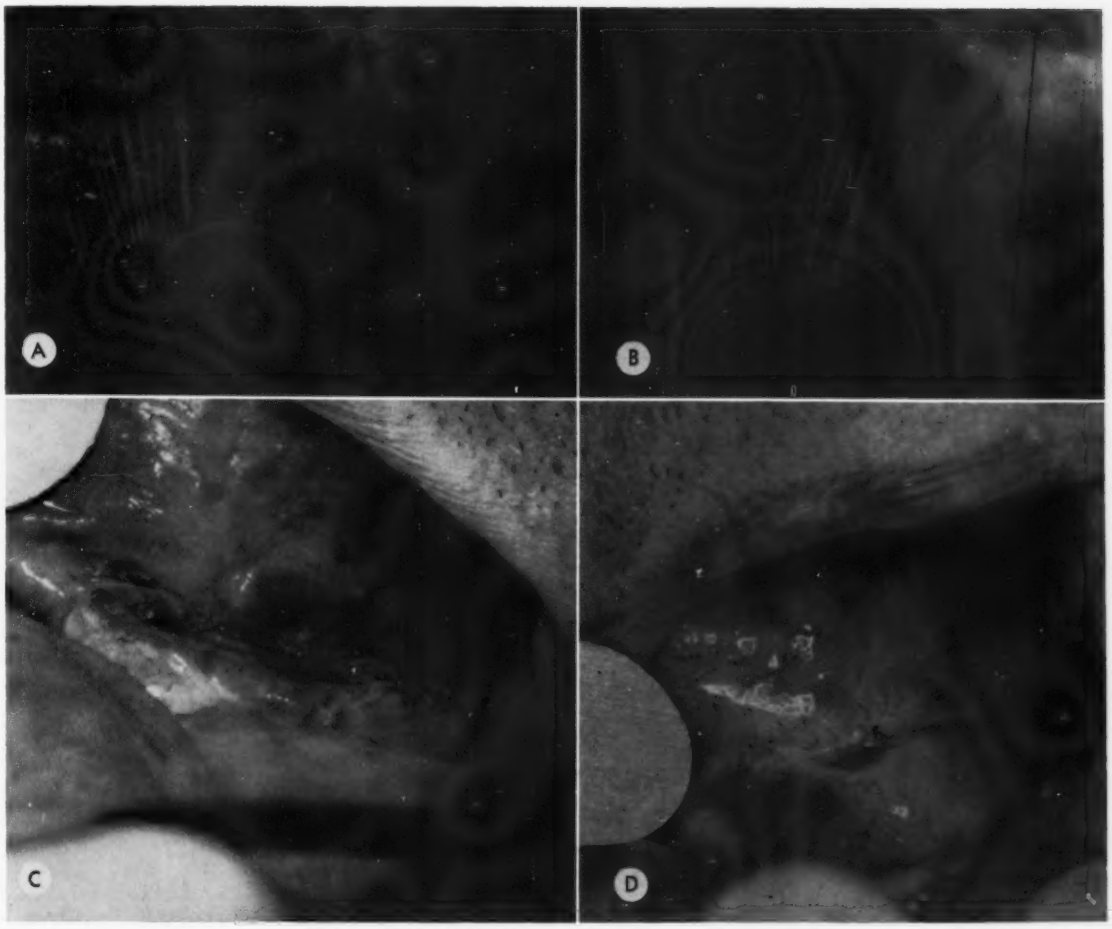


Fig. 20. B.R. 57 W M. *Squamous cell carcinoma of the left side of the floor of the mouth, ulcerated and infiltrating.* A 1 cm. lymph node was palpable in the submaxillary area. Interstitial treatment with radium was indicated.

(*A* and *B*) A double implant was used: a volume implant through the tongue covering the whole lesion, and a submaxillary single plane implant of full-intensity needles. The lesion was tagged with silver clips. The patient was restless and developed progressive edema and a hematoma of the tongue. On the third day a repeat roentgenogram showed marked displacement of the tongue needles upward; the silver clips were now at the lower end of the needles indicating inadequate coverage of the lesion. The implant was removed and treatment was completed with telecobalt therapy. The radium implant delivered 3,100 r in 72 hours and the telecobalt therapy 4,000 r tumor dose in 3 weeks. The duration of the treatment was 4 weeks.

(*C*) Lesion before treatment. (*D*) The lesion regressed completely but recurred 1 year later. A commando-type of operation was performed, and, presently, 2½ years after the first treatment, the patient is free of disease.

GROUP 3. Generally, half of the total dosage is delivered by the external irradiation and half by the interstitial irradiation, here again not exceeding a total of 6,500 r except in cases of very large tumors or in some adenocarcinomas where an extra dose (up to 1,000 r) is delivered to the core of the tumor.

COMMENT

The procedure of combined therapy is particularly useful in centers where supervoltage therapy is not available. In many lesions of the oral cavity and oropharynx, it is difficult and often even impossible to deliver a lethal tumor dose by external irradiation alone without overtaxing the skin, particularly in cases of well-differentiated large squamous cell carcinomas or adenocarcinomas. The addition of interstitial therapy may offer the only possibility of achieving a therapeutically significant dose. This is particularly true in lesions of

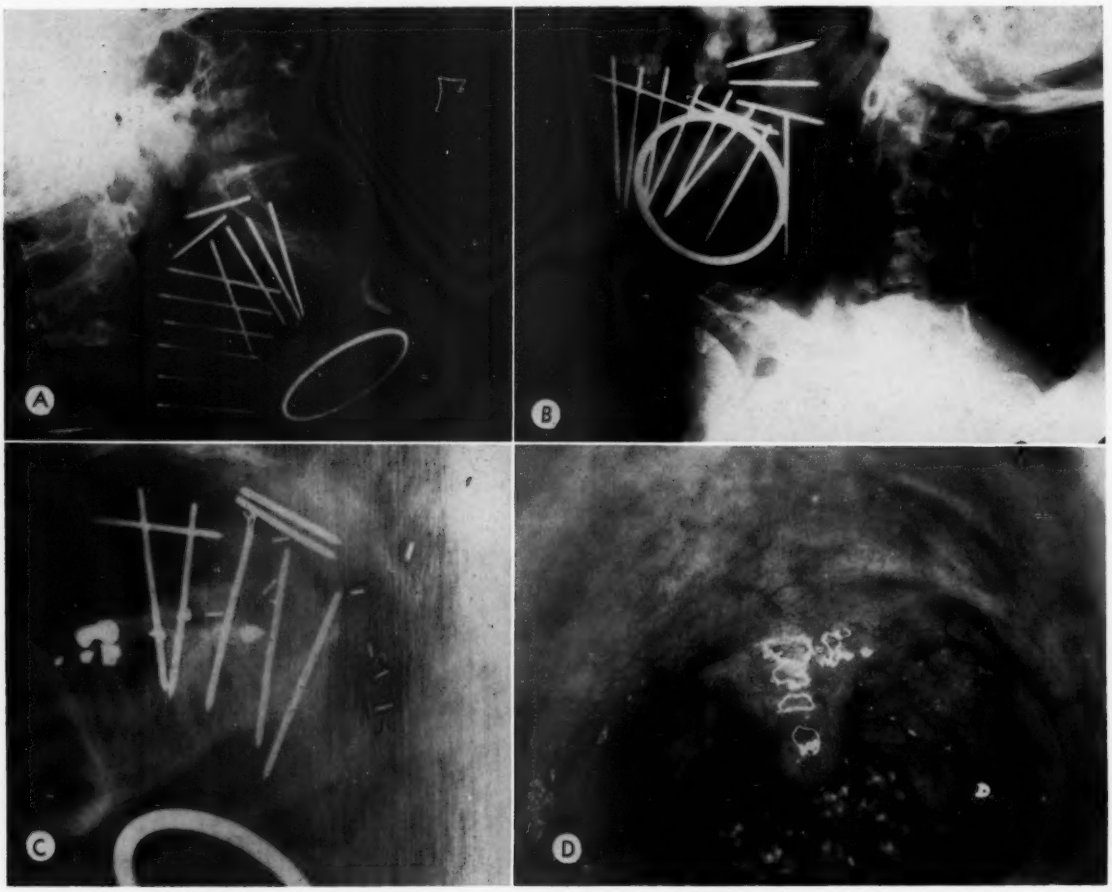


Fig. 21. *Tonsillar and peritonsillar tumors* (true tonsillar, palatoglossal and glossotonsillar areas, and faucial pillars). This is an important group of tumors for combined therapy because they occur relatively frequently and since they are laterally placed they are well suited for the technique described. The external beam portion of the irradiation is, in general, the same for all cases: a single field covering the tumor and its extension, actual or potential. In cases with a large transverse diameter or with the tumor approaching the midline, 2 parallel-opposing fields are used, generally with differential loading (2:1 in favor of the diseased side). This arrangement is chiefly used when only conventional therapy is available. The interstitial therapy will vary depending upon the original site of the tumor and its extensions. The following are the types of implants commonly used:

(*A*) For very early lesions of the anterior pillar, palatoglossal sulcus with or without extension to the proximal portion of the soft palate, we use an implant as shown in *A*. The crossing needles are generally shared between tongue and soft palate. The neck portion is added only if lymph node metastases are present.

(*B*) For extensive lesions of the previous group and especially for tumors of the glossotonsillar area which (usually) have a large extension into the tongue, implants as shown in *B* are used. The portion of the implant in the tongue or soft palate will vary according to the extent of the tumor. Very often a double plane is necessary for the tongue implant. The most posterior needle is inserted in the anterior pillar. Whenever necessary, some additional needles or seeds are implanted in the posterior pillar, buccinator area, retromolar trigone, or buccal mucosa.

(*C*) For the true tonsillar lesions or for the rare posterior pillar tumors, the implant should project more posteriorly due to the common extension of the disease in this direction. We have tried to extend the implant with radium needles, but they were difficult to place and more difficult to keep in the correct position. Presently we implant gold or radon seeds in 1 or 2 rows as needed; 1 row in the posterior pillar and the second in the angle formed between the posterior and lateral walls of the oropharynx as shown in *C*.

*Dosimetry*. For early tumors we deliver 3,000 r tumor dose in 2 to 3 weeks by telecobalt or conventional beam therapy, and 3,500 r with interstitial radium. For more advanced tumors the dosage has been 3,500 to 4,000 r tumor dose in 3 to 4 weeks with external therapy and 3,000 to 3,500 r with interstitial therapy.

(*D*) The acute reaction produced by this type of treatment is very well tolerated, and the late changes are minimal. The most salient feature is the conservation of the mouth moisture as shown in *D*, a patient treated as described 3 years previously for a squamous cell carcinoma of the tonsil.

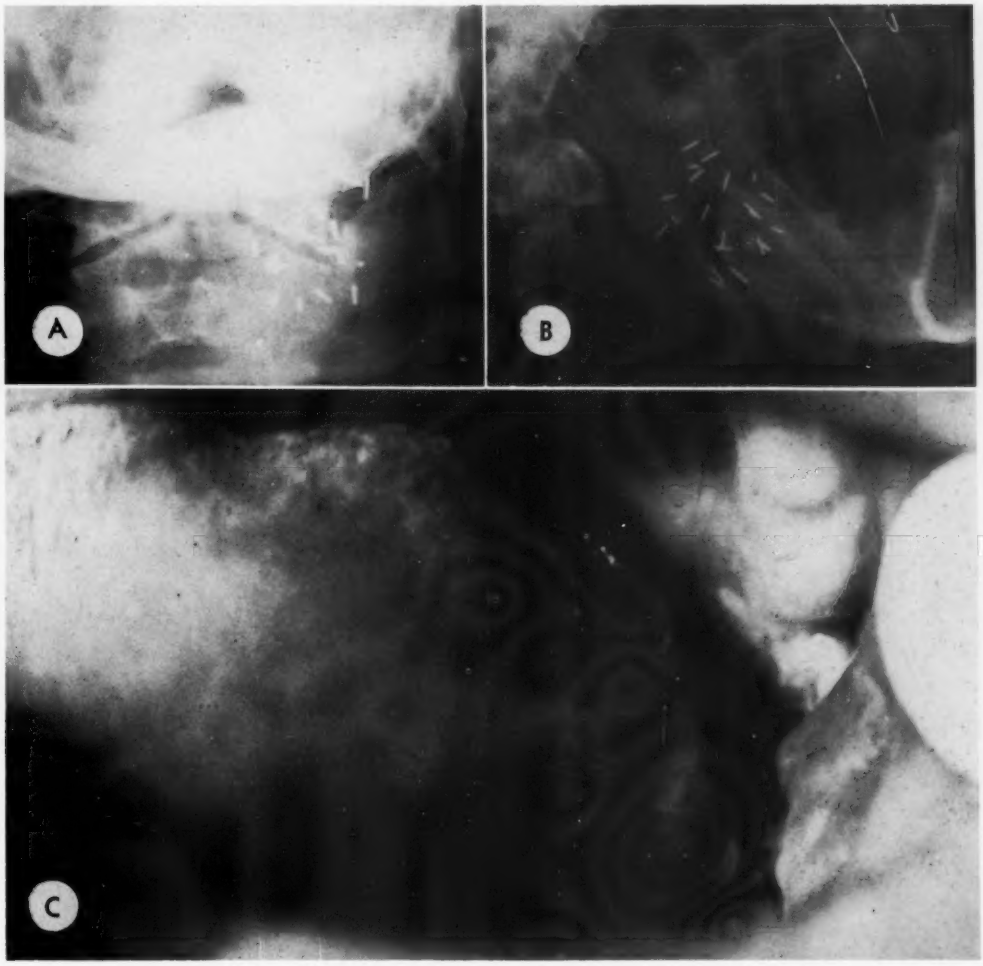


Fig. 22. A.K. 69 W M. *Squamous cell carcinoma of the left buccinator sulcus, with extension to the buccal mucosa, retromolar trigone and soft palate.* The lesion was deeply infiltrating with a necrotic base. No lymph nodes were palpable. A combined treatment by telecobalt therapy and radon seed implantation was planned. The external irradiation was delivered through a single field.

(*A* and *B*) The implant with radon seeds was of a single plane pattern, following Paterson-Parker distribution. The seeds were inserted in the lateral aspect of the tongue, soft palate, and anterior buccal mucosa and retromolar trigone. The dose was: telecobalt therapy: minimum of 4,400 r tumor dose in 4 weeks; radon implant: 2,000 r at 1 cm. from the plane of seeds.

(*C*) Lesion before treatment. The patient developed a rather brisk, slowly regressing mucositis. The ulceration in the area of disease took 8 months to heal. Repeated biopsies showed it to be free of tumor. The patient died of a cardiovascular accident 18 months after treatment, free of tumor.

the base of the tongue, peritonsillar and tonsillar tumors, and extensive lesions of the floor of the mouth with invasion of the gum and of the retromolar trigone. In laterally placed lesions this is a better technique than using a single field or two parallel opposing fields with external beam therapy.

In centers where supervoltage therapy is available, it is not an indispensable method of treatment, but it is no doubt a more rational technique and one which is closer to that ideal of radiation therapy which seeks for specific irradiation of the tumor bearing tissues.

It is very gratifying to see that patients treated by this combined approach, especially those in Group 3, have a greatly improved tolerance to the treatment. This outstanding feature is best demonstrated in

Fig. 23. L.R. 45 W M. *Squamous cell carcinoma of the most posterior portion of the medial aspect of the left lower gum, attached to bone without invasion of it.* A combined technique of 220 kv. roentgen rays, single field, and single plane radium implant was used.

(*A* and *B*) The implantation was performed in the most posterior portion of the lateral aspect of the tongue opposite the lesion. Two additional full-intensity needles were inserted in the soft palate to cover an extension of the tumor. With 220 kv. roentgen rays, a tumor dose of 2,000 r was delivered in 2 weeks. With the implant, 5,500 r was delivered at 0.5 cm. and 3,000 r at 1 cm. in 104 hours.

(*C*) Lesion before treatment. One year after treatment a necrotic ulcer developed in the lower gum with bone necrosis. Partial mandibulectomy was performed 2 years after treatment with complete healing. The patient is free of disease 4 years after therapy.

*Comment.* This was our first patient treated by a combined approach; the dose was probably too high and the treatment insufficiently protracted.

the follow-up where marked difference can be appreciated in late changes; the mouth remains moist and the skin and mucosal changes are minimal.

The sources of irradiation used in our cases have been either radium needles, radon seeds or a combination of both, depending upon the anatomic site of the lesion. In tonsillar or peritonsillar tumors, the posterior portion of the area (posterior pillar, lateral and posterior pharyngeal walls) is implanted with radon or gold seeds because of the difficulty in keeping needles in place in this region; the remainder of the implantation is performed with needles in the lateral portion of the tongue. The crossing needles are implanted in the tongue and soft palate.

The dose levels must be carefully planned and calculated. The ones we suggest are considered safe. In our first group, in which we tried to deliver a total dose of 7,000 r or more, the incidence of necrosis was high.

The cure rate so far obtained has been very promising, and, in some patients who developed a second primary lesion within the oral cavity or elsewhere in the head and neck, a second treatment by radiation has been possible without untoward consequences.

SUMMARY

A combined technique of treatment of head and neck tumors by external beam and interstitial therapy is described. The main advantage of this technique is that the volume of tissue irradiated to a high dose is reduced. This combination is possible in three different ways: (1) interstitial gamma therapy used as a complement of external beam therapy; (2) external beam therapy used as a complement of interstitial radium therapy; and (3) external beam therapy and interstitial irradiation used as agents of equal importance.

The main indications and usual doses delivered by this procedure are given. Combined therapy is very useful in centers where only conventional therapy is available, but, even in centers where supervoltage therapy is in use, this treatment offers a better solution to many problems. The immediate and late reactions to the treatment are diminished.

It is possible that by such a planned technique the results in some cases of head and neck tumors could be improved and the side effects and complications diminished.

Details of techniques, dosimetry, indications and examples are given.

## PART IV. UNUSUAL RADIUM IMPLANTS IN THE TREATMENT OF CANCER

One of the main objections to interstitial gamma-ray therapy already mentioned is the lack of versatility allowed by this technique. It is granted that its applications are limited, for many radiosensitive tumors do not lend themselves to treatment by interstitial therapy. Some of the contraindications conventionally accepted are: (1) large volume or very anaplastic tumors; (2) inaccessible areas; and (3) lesions close to or involving bone or cartilage.

There are patients with tumors of the well-differentiated group (squamous cell or adenocarcinoma) in whom treatment by external irradiation is difficult because a large volume of normal tissue must be irradiated in order to reach the tumor, because it is impossible to avoid irradiation of sensitive structures or because it is difficult to get enough dose at the depth of the tumor. Some of these cases can be satisfactorily treated by interstitial therapy.

It is our intention to demonstrate that a wider use of interstitial therapy is possible, even under unusual circumstances to the benefit of some patients who would pose difficult problems of technique if they were to be treated with external beam therapy alone.

Implants may be termed unusual when they are placed:

1. *Through bone or cartilage.* It is often stated that radium implantation through or near bone or cartilage is fraught with a very high incidence of necrosis and, therefore, should be avoided. Our experience, over more than a seven year period in treating a

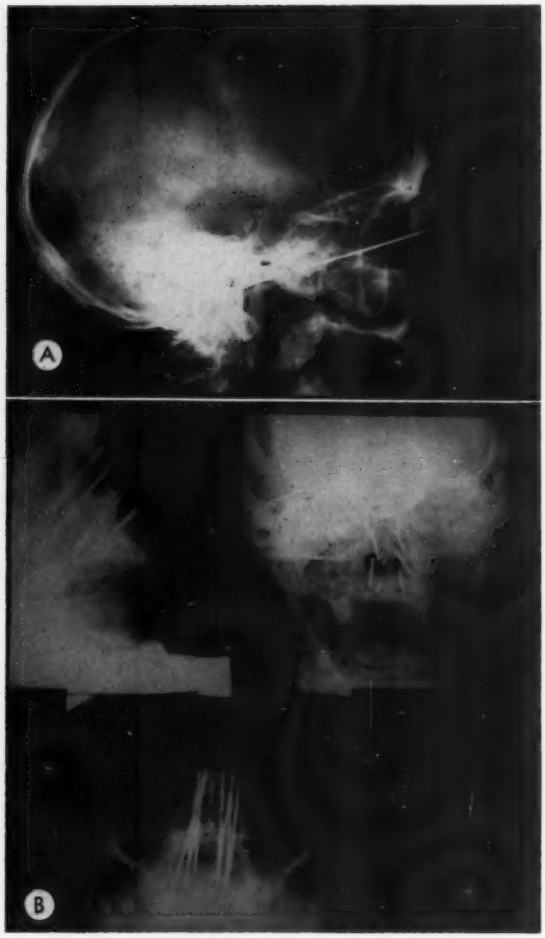

Fig. 24. *Ethmoid implant.* (*A* and *B*) This is a double plane implant, which is a modification of the single plane implant as developed by Dobbie in Manchester. It is felt that this modification enlarges the area irradiated without increasing the dose close to the implant to dangerous levels. It is indicated in cases of early squamous cell carcinoma of the nasal septum, in cases of esthesioneuroepithelioma as a complement of external irradiation in extensive tumors of the ethmoid, and in postoperative ethmoidal recurrences after combined surgical and radiation therapy of maxillary antrum tumors. It must be realized that the indications for radium alone must be precise and that only small well-differentiated tumors can be so treated.

*Treatment technique.* The implant is always of a double-plane pattern using crossing at the outer end, or dumbbell or Indian club type needles, depending upon the site of the primary lesion in relation to the surface. In general, the separation between planes is 2 cm. The day prior to the implantation a roentgenogram is taken with a straight wire placed on the lateral aspect of the face, directed from the top of the bridge of the nose to the upper edge of the tragus. This generally follows the base of the skull as shown in *A*. The skin is marked with a line following this direction. This line is used during the implantation as a landmark, and the needles are implanted parallel to it. The implantation is started with the upper two needles which, in general, are placed on both sides of the bridge of the nose in the orbits, through soft tissues, above the level of the cribriform plate. A portable roentgenogram is taken to see if the position of the first needles is satisfactory; if it is, the whole implantation is performed parallel to these needles, boring the nasal bones with a drill whenever the implantation is done through bone. Dummy needles (made of stainless steel wire) are used during the whole procedure, and, if their position is satisfactory, they are replaced by the radium implant at the end of the procedure.

*Dosage.* If the treatment consists of interstitial therapy alone, we deliver a maximum of 7,000 r and a minimum of 5,000 to 5,500 r for squamous cell carcinomas. If it is to be complemented by external irradiation, the dose will vary with the particular case. The treatment was well tolerated in more than 10 cases so managed. *B* shows a patient of very advanced age (82 years old) with a small squamous cell carcinoma of the nasal septum, which is marked by silver clips.

considerable number of cases, does not bear out this statement. Bone and cartilage will tolerate an implant well, provided a uniform distribution of the sources is obtained and proper dosimetry is used. More than a score of patients so treated have had several years of follow-up without a single complication. Therefore, the proximity of bone or cartilage is not a valid contraindication to interstitial therapy (Fig. 24, 25, 26, 27 and 28).

2. *In anatomic sites which are not commonly implanted with or without complex arrangement of the radium sources.* The perineum, groin and pubis are areas where postoperative recurrences are not infrequent after the treatment of tumors originating in the vulva, penis, bladder and rectum. They manifest themselves as cutaneous or subcutaneous masses, often multiple, in the operative field and probably represent seeding of the tumor as a result of surgical manipulation. Some of these may be controlled by proper radiation therapy (Fig. 29, 30 and 31). These lesions are difficult to manage by external irradiation alone unless a large volume of tissue is irradiated, in which case a cancerocidal dose may not be tolerated. Some of these tumors are adenocarcinomas requiring very high doses for sterilization.

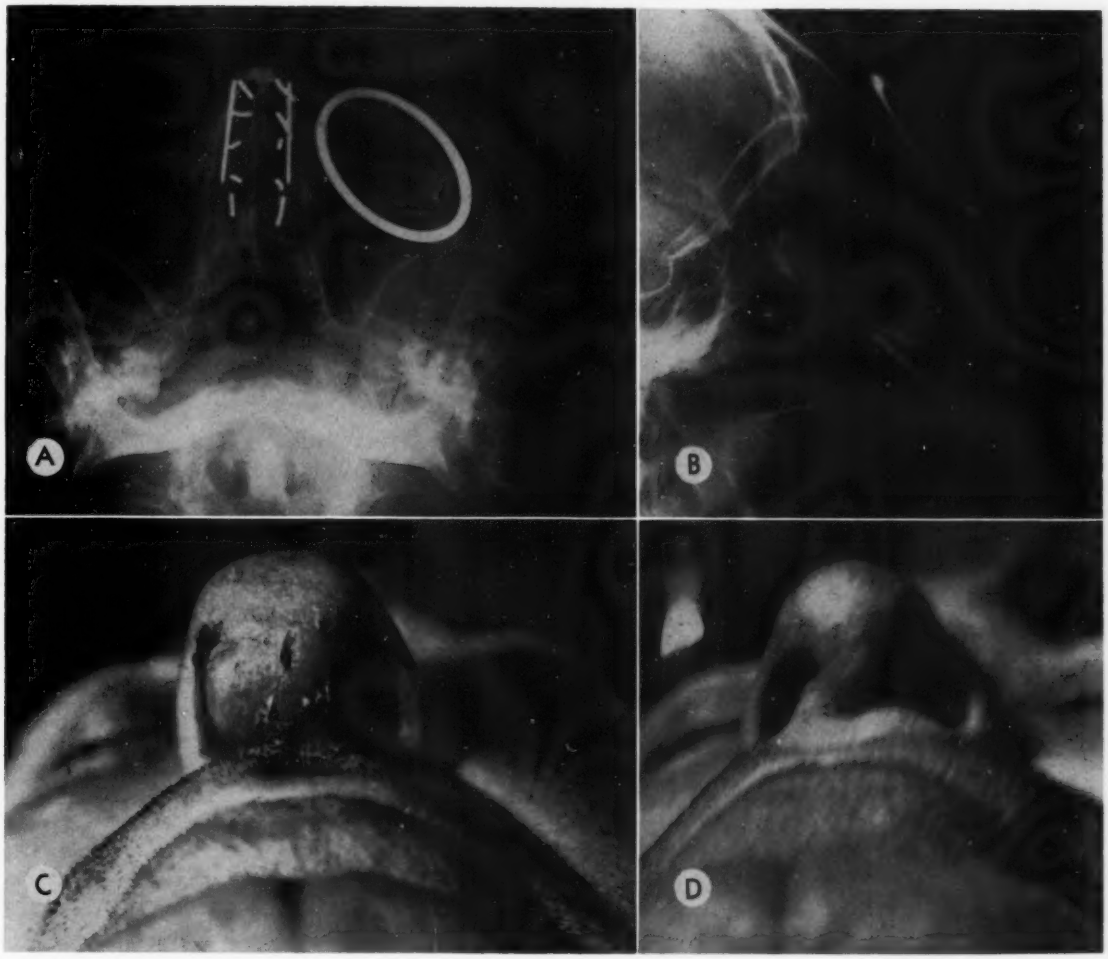


Fig. 25. A.K. 60 W M. *Squamous cell carcinoma of the columella involving the lower portion of the nasal septum, the tip of the nose, and the medial portion of both alae nasi.* It was decided to use interstitial radium alone.

(*A* and *B*) A double-plane implantation was performed. Crossing needles were used at the outer ends of the planes. Most of the needles went through cartilage. The dose delivered was estimated as a maximum of 6,500 r and a minimum of 5,600 r. The treatment time was 112 hours.

(*C*) Lesion before treatment. (*D*) The treatment was very well tolerated. A good cosmetic result was obtained. The patient has been free of disease for 18 months.

3. *In surgically exposed areas.* The classic indications for interstitial gamma-ray therapy can be considerably enlarged if enough ingenuity is used in devising proper geometric arrangements of the radiation sources and by making some lesions accessible by surgical procedures, such as: episiotomy, pharyngotomy, cystotomy, laparotomy, etc. These are cases where interstitial radiation through a surgical incision can solve a difficult therapeutic problem. It is common practice in the treatment of carcinoma of the bladder. Figure 32 is an example of residual disease in the bladder after roentgen-ray therapy, treated in this manner. This technique may also be indicated in some exceptional cases of tumors ordinarily considered inaccessible, *i.e.*, pelvic tumors through a colpotomy (Fig. 33) or some residual or recurrent tumors of the posterior wall of the pharynx through a lateral pharyngostomy.

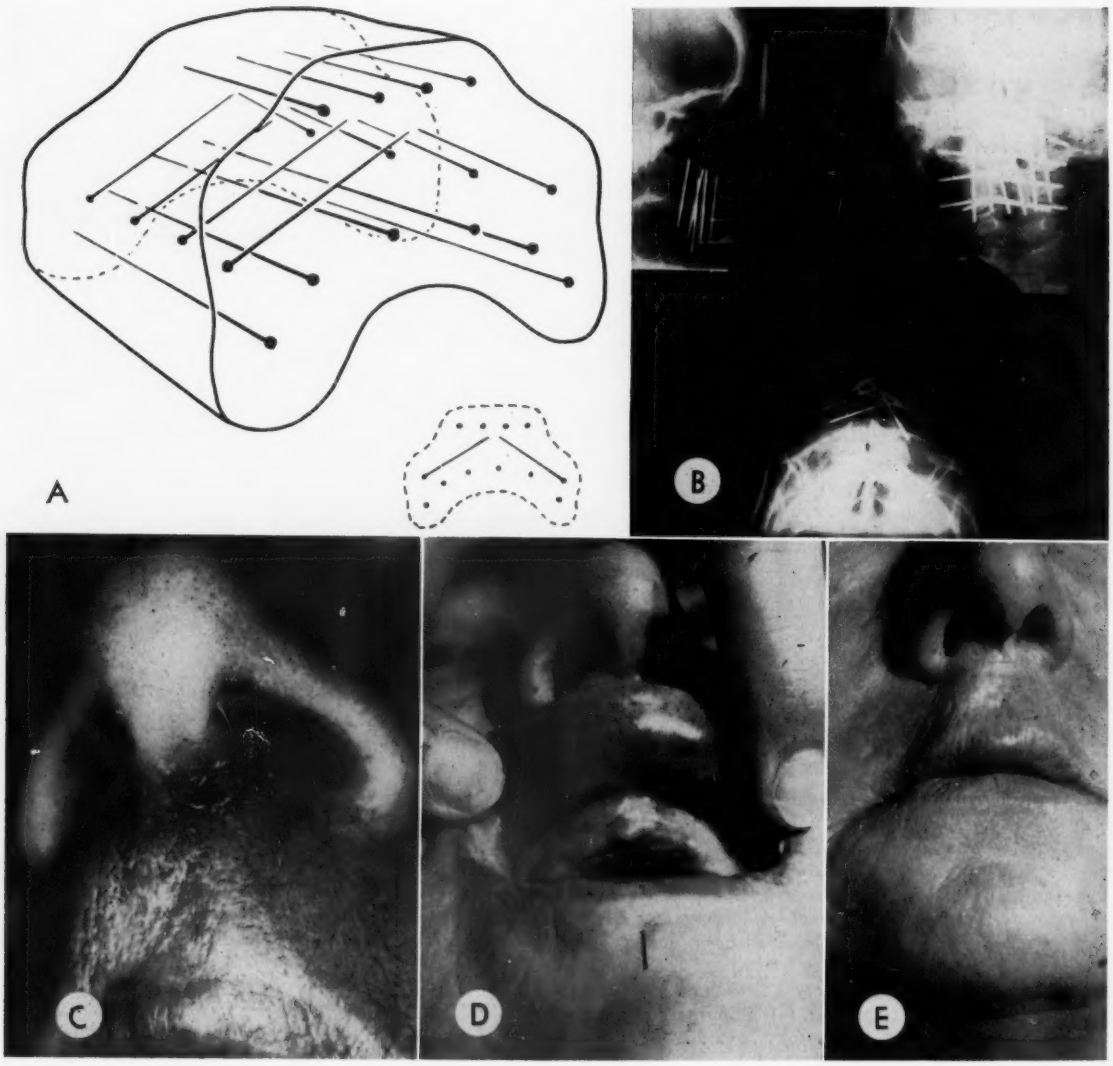


Fig. 26. E.E. 64 W F. *Squamous cell carcinoma originating in the columella involving the lower portion of the nasal septum, both alae nasi, upper lip in its whole thickness, and the upper gingivolabial sulcus.* No lymph node metastases were palpable. It was decided to use interstitial radium alone, complex pattern type.

(*A* and *B*) The implant consisted of 3 planes of radium needles. The deepest plane was implanted through the bone of the upper alveolar ridge, behind the tumor; the middle plane was inserted through the upper lip and included both alae nasi. The superficial plane was implanted in the dorsum of the nose. The last two planes went through or very near cartilage. A very uniform volume of irradiation was obtained, as shown in *A*. The estimated dose was 5,500 r delivered in 100 hours.

(*C*) Lesion before treatment. The treatment was very well tolerated. The mucositis in the nose was confluent and a wax mold was kept in each nasal cavity for 3 weeks in order to prevent adhesions. (*D* and *E*) The therapeutic and cosmetic results were excellent. The patient is free of disease after 18 months.

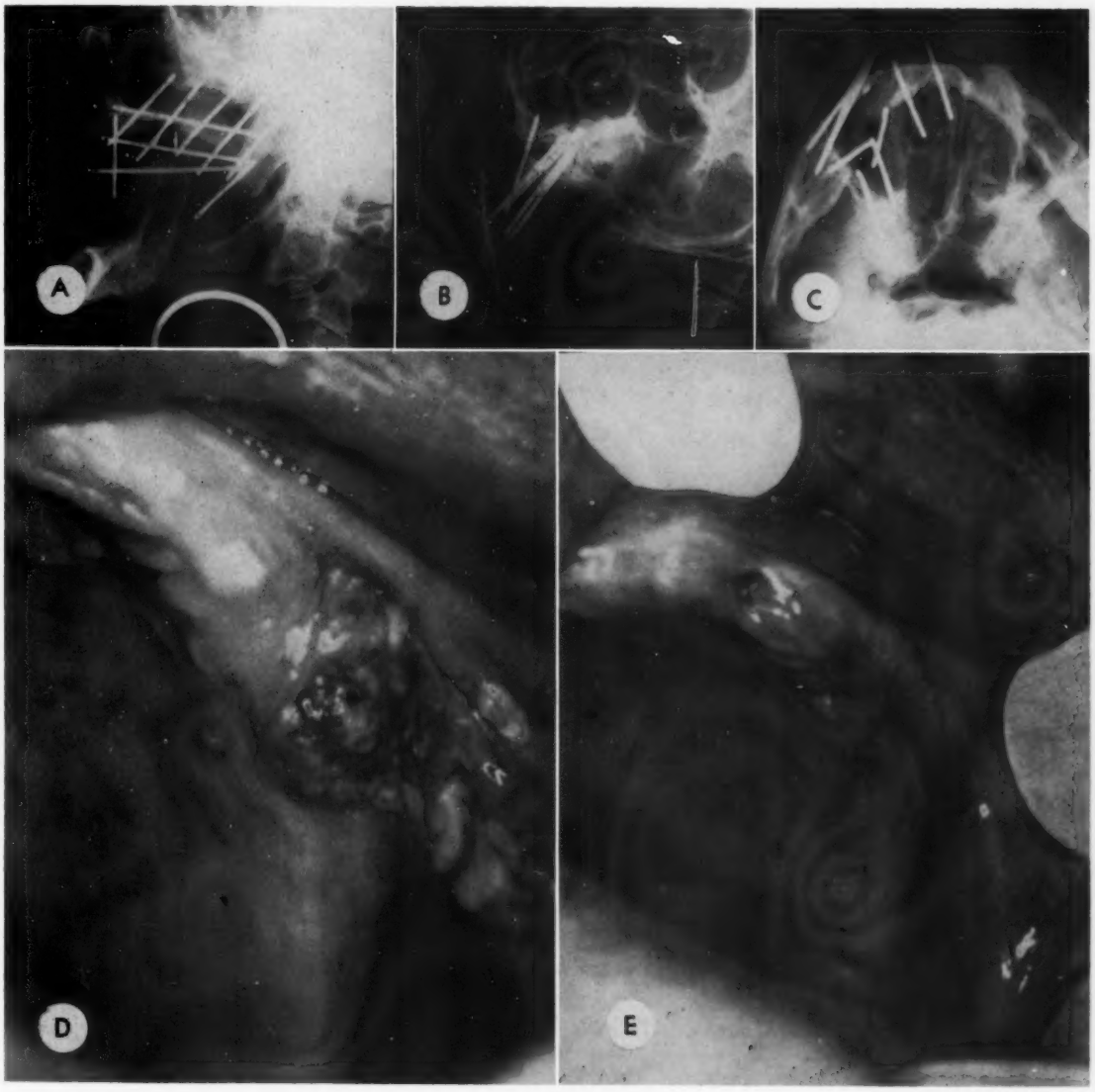


Fig. 27. W.C. 73 W M. *Squamous cell carcinoma of the upper gum with invasion of the adjacent bone and extension to the upper gingivobuccal sulcus and buccal mucosa.* No lymph nodes were palpable. Interstitial radium alone was used.

(*A*, *B* and *C*) An angulated 2-plane pattern implant was applied with the inner plane going through the upper alveolar ridge into the cavity of the maxillary antrum. The outer plane was implanted through the buccal mucosa into the soft tissue of the cheek. A maximum of 7,500 r and a minimum of 6,000 r was estimated as the dose delivered during the 120 hours the implant remained in place.

(*D*) Lesion before treatment. (*E*) The patient developed a brisk, confluent mucositis of the treated area which healed quickly after the treatment. There was good healing of the mucosa and bone. The dimple in the upper gum is one area which is recessed, not perforating, and well epithelized. The patient is free of disease 19 months after treatment.

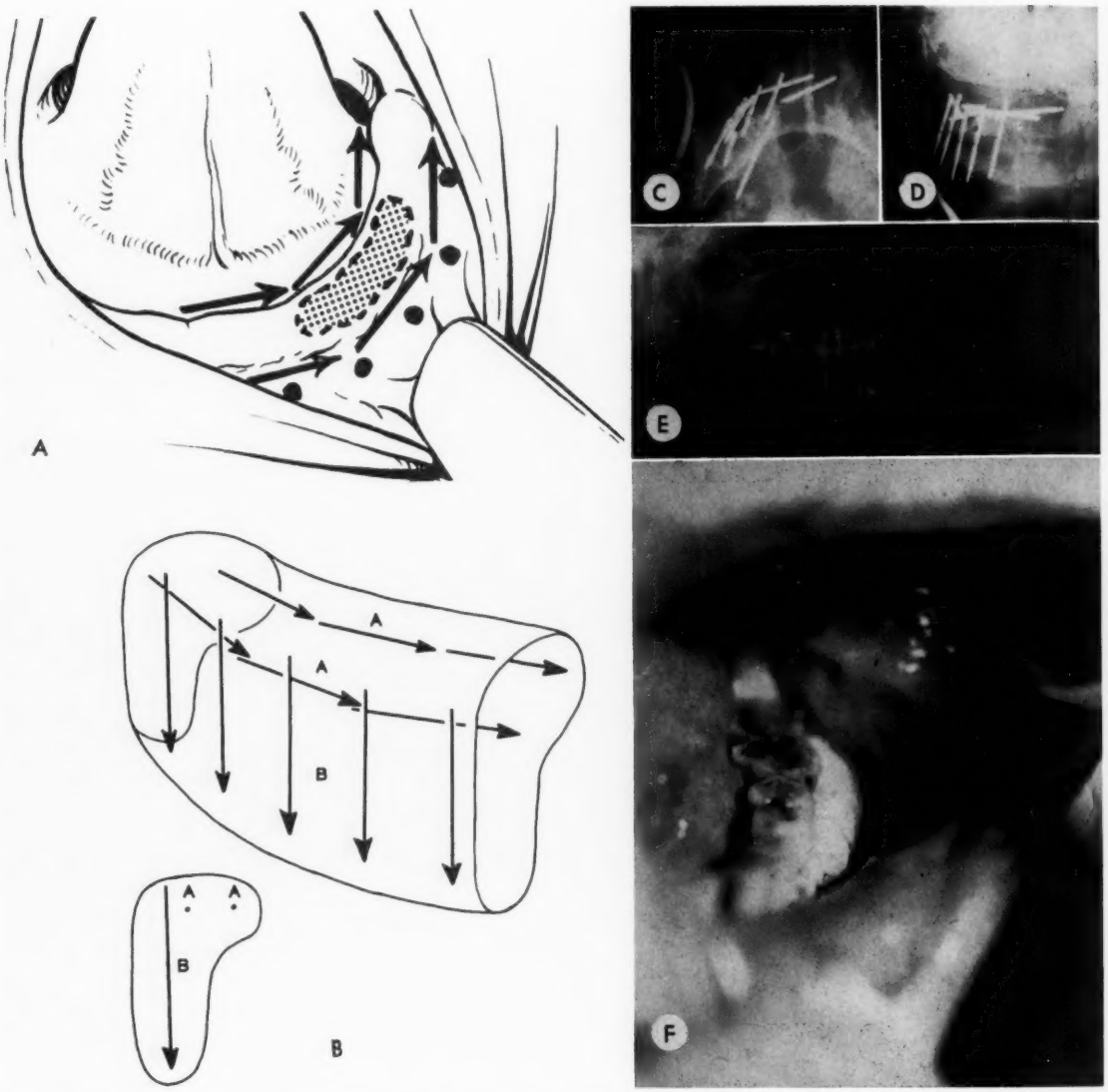


Fig. 28. C.R. 75 W F. *Squamous cell carcinoma of the left gingivobuccal sulcus with invasion of the adjacent lower gum (including bone) and buccal mucosa.* The lesion was on a leukoplakic background. The patient had been a "snuff-dipper" for many years. No lymph nodes were palpable. The teeth were in poor condition and some were loosely imbedded in the tumor; they were removed before treatment. Combined treatment by telecobalt therapy with a single field and interstitial radium was planned.

(*A-E*) The interstitial therapy consisted of a complex pattern composed of 2 right angle plane implants, the vertical plane going through bone and the horizontal plane inserted in the mucosa of the gum covering the whole tumor and th e patches of leukoplakia, as shown in the sketches (*A* and *B*). At the time of the implant the residual tumor was represented only by an ulceration in the gum as shown in the sketch (*A*). The dose of the external beam radiation was estimated at the tumor to be 4,500 r delivered in 4 weeks. With the implant a dose of 2,500 r was planned, but the patient pulled the needles out after 1,500 r had been delivered in 48 hours, and refused to have further treatment. The reaction was mild.

(*F*) Lesion before treatment. After 4 months of complete healing recurrence developed in the area. The recurrence was small in the bone with ulceration of the mucosa of the lower gum. The patient refused surgery.

*Comment.* The treatment was obviously insufficient for a well-differentiated squamous cell carcinoma invading bone which probably would require 7,000 to 8,000 r total dose to be controlled.

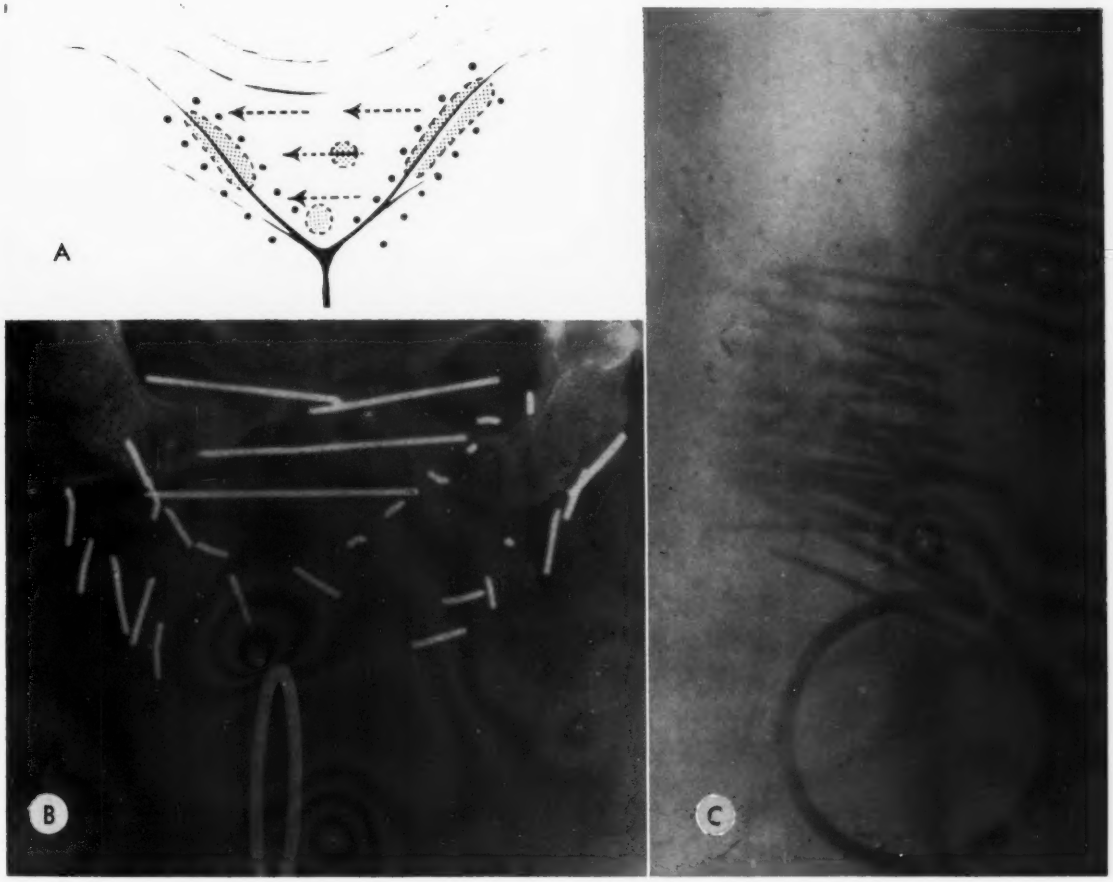


Fig. 29. M.W. 50 N F. *Recurrent cutaneous and subcutaneous tumor after total vulvectomy and bilateral groin dissection.* Combined 220 kv. of roentgen therapy and interstitial radium was indicated.

(*A*, *B* and *C*) An implant of the complex pattern type was used. The folds of the groin were sutured together on each side to ensure that the whole area would be included within the two planes. A single plane was used to irradiate the cutaneous tumors in the mons veneris. A tumor dose of 4,000 r in 5 weeks was given with conventional therapy. An additional 3,000 r in 100 hours (average) was delivered by interstitial radium 2 weeks after the external irradiation was completed.

The treatment was well tolerated. The patient developed a perianal recurrence 1 year later, which was treated by a volume radium implant, and is now free of disease 2 years after the treatment.

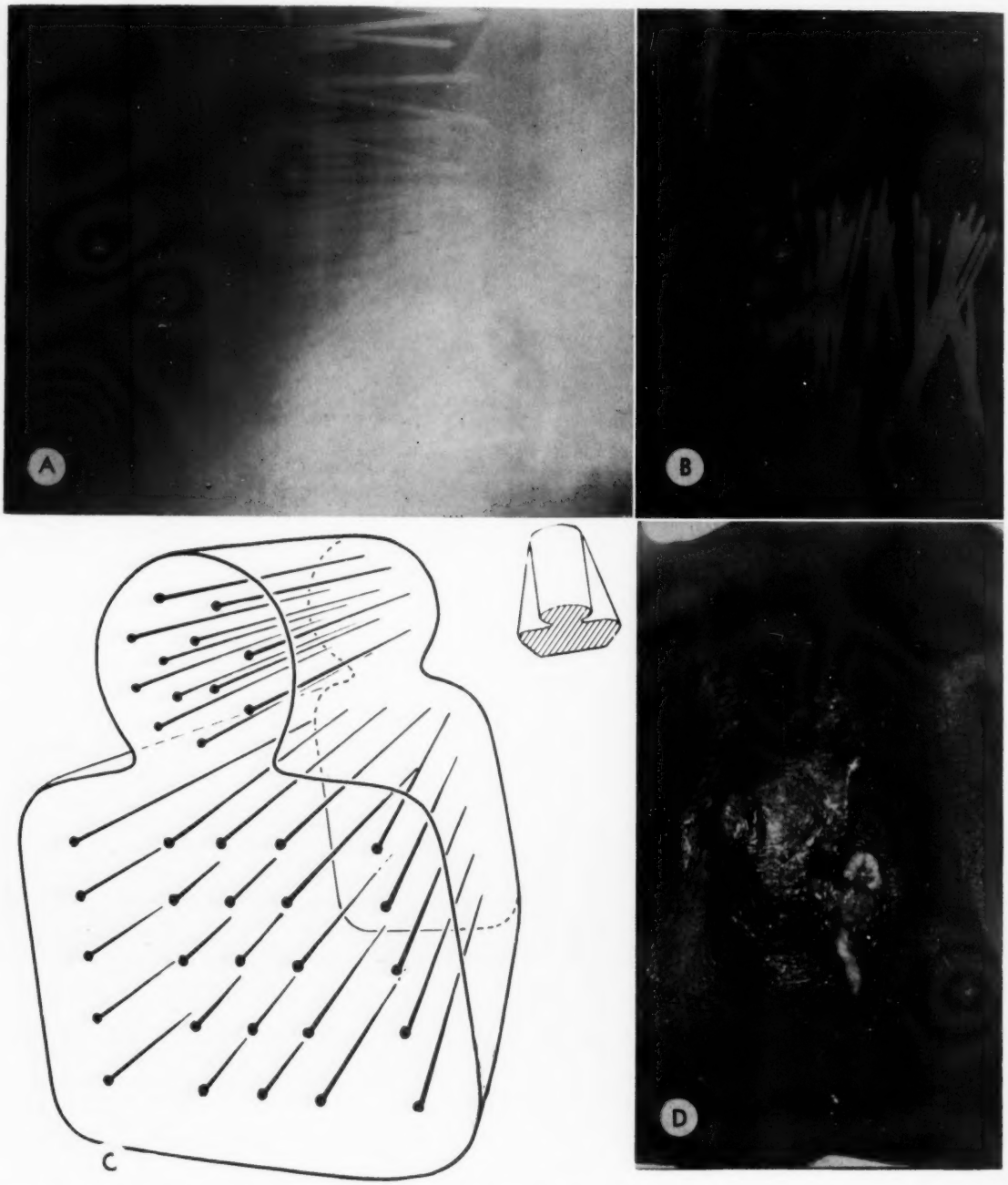


Fig. 30. M.C. 48 N M. *Recurrent squamous cell carcinoma after radical amputation for carcinoma of the penis.* It was decided to use combined 220 kv. roentgen therapy and radium implantation.

(*A*, *B* and *C*) The radium implant was of a double volume pattern. A tumor dose of 3,000 r in 3 weeks was delivered by external irradiation, and 4,000 r in 48 hours by the radium implant.

(*D*) Lesion before treatment. The tolerance was good and the mass disappeared leaving a urethral fistula. When seen 4 months later, the patient had no obvious tumor; he died 6 months after therapy of unknown causes.

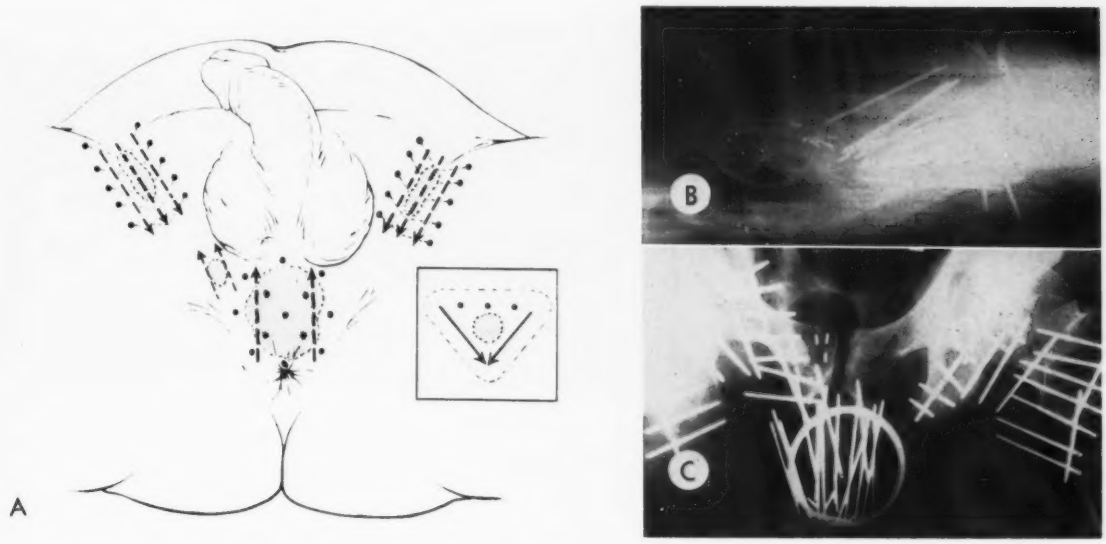


FIG. 31. J.G. 54 W M. *Multiple recurrences of carcinoma of the bladder 4 years after total cystectomy and radon seed implantation in a prostatic extension.*

(*A*) Sketch showing site and extension of the disease and the planned radium pattern. A palliative treatment was indicated because of the slow evolution of the process.

(*B* and *C*) A complex pattern radium implant was used consisting of a volume and small single plane in the perineum, and a 3-plane triangular arrangement for each groin. A dose of 6,000 r was delivered by the volume implant and 5,000 r to each groin by the triangular arrangement in 96 hours.

The treatment was well tolerated and all the lesions disappeared. The patient died 6 months later with distant metastases but with the treated lesions under control.

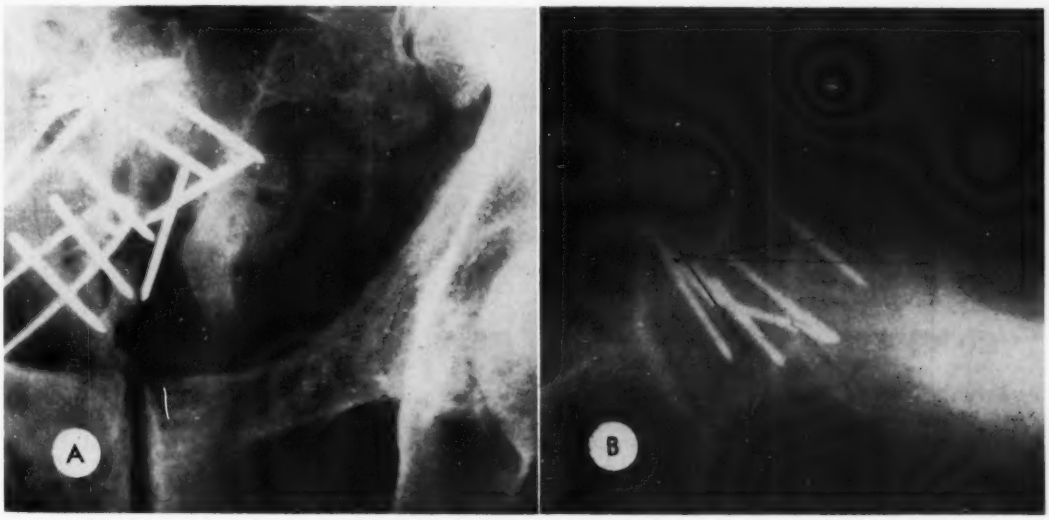


FIG. 32. *Residual carcinoma of the bladder following roentgen therapy.* (*A* and *B*) An interstitial radium implantation was performed through a cystotomy.

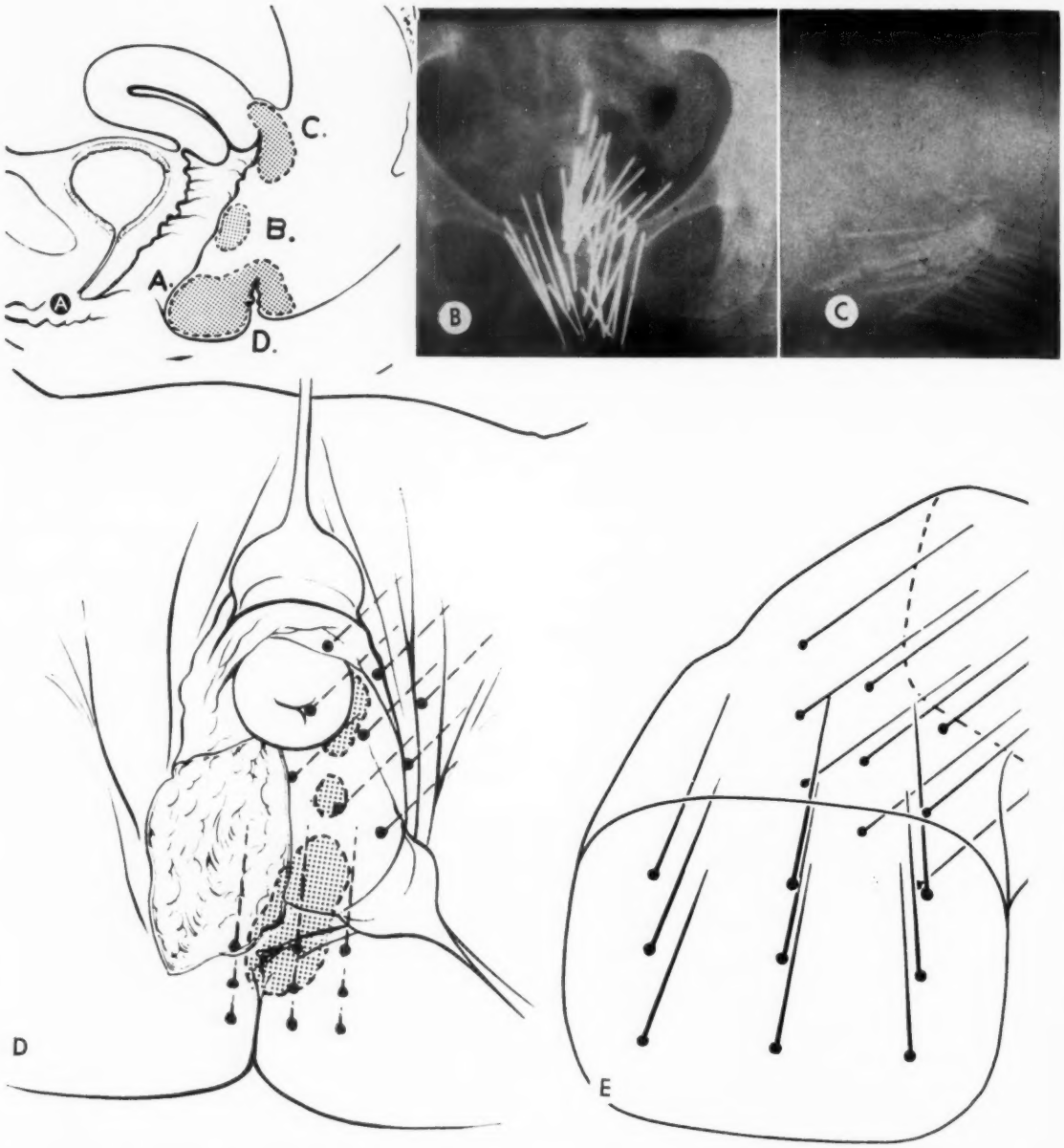


Fig. 33. E.F. 45 W F. *Multiple recurrences from an adenocarcinoma of the rectum, 6 months after a Miles' operation, with resection of the posterior vaginal wall.*

(*A*) Location of recurrences. The vagina was so narrowed as to prevent proper implantation being carried out. It was decided to use interstitial radium therapy alone. A colpotomy was necessary in order to reach the upper masses (*D*).

(*B* and *C*) A complex pattern implantation composed of 2 volumes was performed partially through the "enlarged" vagina and partially through the skin of the perineum. A tandem was inserted in the uterus to increase the dose medially. The volume of irradiation obtained is shown in idealized form in *E*. The dose delivered was estimated to be between 6,000 and 7,000 r in 94 hours.

The patient had a fair reaction with delayed healing of the colpotomy and is presently free of tumor after 16 months.

## CONCLUSION

Some of the objections to interstitial gamma therapy are valid ones, but it is also true that if the same enthusiasm and ingenuity that have been devoted to the development of external beam irradiation were applied to this field, interstitial therapy would be more widely employed and the objections against it reduced. The examples cited illustrate that interstitial gamma-ray therapy can be used even where indications are unusual, obtaining good results with a minimum of late changes and without undue complications.

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# RADIATION TREATMENT OF CANCER OF THE MOUTH, PHARYNX, LARYNX AND NECK*

## A RECORD OF SUCCESSFUL RESULTS

*By* D. CATLIN, M.D.
NEW YORK, NEW YORK

### INTRODUCTION

IT IS the purpose of this paper to present a concise, factual record of successful results obtained by radiation therapy in several forms of head and neck cancer treated at Memorial Hospital during the twenty-four year period from 1931 through 1954. It is furthermore purposed to make a practical analysis of these successful treatment techniques and dosages. There is little value in dwelling on methods which have never succeeded.

Fractionated radiation therapy of head and neck cancer began at Memorial Hospital in 1931. At that time we knew nothing of the dosage factors used by others as such data had not been published. We did know that roentgen therapy given in daily doses over a period of three to six weeks produced an intense reaction in the irradiated tissues, followed by gradual healing and, in some instances at least, by a complete disappearance of the tumor.

In the beginning our treatment was planned mostly by guesswork. As time went on those techniques which succeeded were retained and those which always failed were discarded. By such a process of trial and error, we have arrived at the successful techniques and dosages described in this report.

At no time during this period has our attending staff assumed that the problem of successful radiation therapy has been solved. The techniques have been flexible; there has always been an element of empiricism in arriving at total dosage and the physical factors employed have been somewhat influenced by the available equipment. New ideas and techniques have and are being constantly applied to special cases. With further understanding of the effects of ionizing radiation on cancer and with improved design in physical equipment, changes and modifications in radiation therapy will be in order. In the meantime, a record of successful treatment methods used in the past has been helpful to us in outlining radiation therapy for patients today.

### SOURCE OF CLINICAL MATERIAL

A careful search of the Memorial Hospital records and of the office records of our attending staff on the Head and Neck Service was made for the years 1931 through 1954. An over-all period of twenty-four years was studied and only those patients remaining alive and free of cancer for five years or more are included. A positive biopsy was obtained from every cancer case recorded in this report. Additional successful cases have been discovered from time to time which were not found in the original search; these cases have been added.

### TYPE OF CLINICAL MATERIAL

As would be expected, the kind of head and neck cancer selected for this study comprises those tumors which were most frequently and successfully treated by radiation. Such cancers were found in the mouth, pharynx, larynx and neck and are listed in the order of their relative frequency in Table 1.

Moreover, the cases recorded here are restricted to those in which the successful end result can be unequivocally credited to

* From the Head and Neck Service, Memorial Hospital, New York, New York.
Presented in part at the Forty-second Annual Meeting of the American Radium Society, San Juan, Puerto Rico, March 17–19, 1960.

TABLE I

HEAD AND NECK SERVICE, MEMORIAL HOSPITAL, NEW YORK CITY

SUCCESSFULLY IRRADIATED CASES

| 1931–1954 Inclusive | Positive Biopsies from All Tumors | |
|---|---|---|
| Cancer of the Tongue | | |
| a. Anterior two thirds | 119 cases | |
| b. Base of tongue | 55 | |
| Subtotal | | 174 cases |
| Cancerous (metastatic) Neck Lymph Nodes | | 113 |
| Cancer of the Tonsil | | 101 |
| Cancer of the Nasopharynx | | 78 |
| Cancer of the Floor of the Mouth | | 51 |
| Cancer of the Extrinsic Larynx | | 50 |
| Cancer of the Soft Palate | | 36 |
| Cancer of the Cheek (buccal mucosa) | | 30 |
| Total | | 633 cases |

radiation therapy alone. A great many more than an equal number of "cures" was obtained by a combination of radiation therapy and surgery or by surgery alone (see discussion on cancer of the tongue in section on Comment on Successful Cases), but, as the successful results could not be attributed solely to irradiation, these patients were omitted. Approximately 100 successful cases were found in which the radiation therapy used was so arbitrary and variable as to make them unsuitable for group analysis; these patients were not included. Also excluded were those patients whose primary cancers in the head and neck were controlled by radiation but who died in less than five years either of other causes or of distant metastatic cancer.

It must also be pointed out here that several fairly common anatomic forms of mouth cancer are not included in this review. Cancers of the lips, gums, hard palate, paranasal sinuses and salivary glands are considered by us to be best treated by surgery; too few of these patients received their initial treatment by radiation to permit any useful group analysis.

Returning now to the patients comprising this study, most of them were afflicted with squamous or epidermoid carcinoma; there were some lymphosarcomas and a very few adenocarcinomas. In general, the histology and grade of the cancers did not influence the amount of treatment given. Usually, it requires large amounts of radiation to destroy any given cancer, regardless of whether it is epidermoid carcinoma or lymphosarcoma. The surprising fact here was that any adenocarcinomas at all were "cured" as most of them are resistant to irradiation. There comes to mind a thirty-three year old patient suffering from a 5 cm. adenoid cystic type of adenocarcinoma in the base of the tongue. This lesion permanently disappeared following the use of rather heavy roentgen radiation and radon seeds (4,550 r × 2 through bilateral 7 cm. lateral ports plus 21.8 mc in two doses of seeds) only to have the patient die seven years later of widespread pulmonary and skeletal metastatic cancer.

All of our successful cases fell within the treatment ranges as described in the sections on Radiation Treatment Techniques. It was interesting to observe that as additional "cured" patients were found in the latter part of our search, they also and almost without exception were within the same ranges. Successful cases treated by us since 1954 mostly followed the same pattern.

## THE SUCCESSFUL CASES

Table 1 is as complete as possible and includes all the successful cases found up to the time of writing this report (February, 1960). The order of listing adheres to the relative frequency of the various anatomic forms of cancer. This list of 633 cases represents in all likelihood the largest collection of successful results by "pure" radiation therapy that we will ever assemble on our Head and Neck Service because of our ever increasing reliance on surgery at some point in the treatment of most of these types of cancer.

Table 1 indicates that cancer of the

tongue was the most common tumor treated. Furthermore, the tongue is divided into its anterior two-thirds and the base, as the treatment techniques for the two areas are different. Also, cancer occurred about twice as often in the anterior part of the tongue.

Most of the 113 patients with metastatic neck lymph nodes also had successfully irradiated cancers elsewhere in the mouth or pharynx. Such patients are listed two or more times, once under each of the respective sites treated. A few patients had two unrelated and successfully treated primary cancers; these patients are also listed twice. Therefore, it can be understood that the total number of cases recorded is actually greater than the number of patients treated. However, in each instance a proved deposit of cancer was treated and controlled.

### COMMENT ON THE SUCCESSFUL CASES

One of the more interesting discoveries to come out of the study of the hundreds of hospital records from which these cases were selected was the regularity with which the various types of successful cases fell into the same recognizable treatment "pattern." It is true that many failures also occurred in these same patterns but only very isolated successes were found outside them. Some cancers are just not curable as yet by any known type of treatment.

It is apparent also that many of these 633 successful radiation cases would now be treated by surgery. During the last two years of this study (1953 and 1954), not a single cancer of the anterior two-thirds of the tongue, floor of the mouth, cheek or extrinsic larynx could be found which was successfully treated by radiation alone. Surgery is being used for most mouth cancers, especially when the lesions encroach on either the mandible or maxilla. Our policy of laryngectomy for all resectable cancers of the extrinsic larynx has improved our five year salvage (based on total experience) from 10 per cent to 30 per cent. Interestingly enough, there were 21 instances during these last two years in which radiation controlled metastatic cancer in neck lymph nodes even though neck dissection is now the preferred treatment.

This list of 633 successful cases is a selected collection and is of no value in determining end results. For example, during the fifteen year interval 1939 through 1953 a total of 1,554 cancers of the tongue was seen with a salvage of 467 cases, representing a gross five year cure rate of 30 per cent and a net rate of 35.4 per cent among the determinate patients. Although our list of successful radiation cases covers the longer interval of twenty-four years, there are only 174 patients with cancer of the tongue. These 174 successful cases comprise only a fragment of our total experience and cannot be used alone to calculate a meaningful end result.

In this study we are concerned exclusively with the good results of radiation. When embarking on a course of radiation treatment for a particular patient, it is useful to have at hand a record of past successes as a guide. This supplies us with a pattern of successful performance; we have found it extremely helpful and will continue to use it until something better is available.

### RADIATION AGENTS, FACTORS AND DATA

As would be expected over a twenty-four year period in a busy hospital in which radiation therapy is given to a great number of patients, the apparatus was both altered and replaced, so that all our cases were not treated with the same equipment. However, the changes were not radical and the general principles of our treatment program remained essentially the same. At its best, clinical radiation therapy is an inexact and empirical treatment method—one of its frustrating aspects.

### ROENTGEN THERAPY

The roentgen therapy machines used in treating the cases in this study are in the high voltage (200–250 kv.) and low voltage (100–130 kv.) category.

*High Voltage Roentgen Rays.* We em-

ployed high voltage roentgen rays on all cancers which lay at or involved tissues at a depth greater than 2 cm. from the surface of the skin or mucous membrane. At the beginning we used a machine operating at 200 kv., filter 0.5 mm. Cu, half value layer 0.9 mm. Cu, and target skin distance 35–70 cm. Later on, some treatment was given at 220 kv., filter 0.5 mm. Cu, half value layer 1.0 mm. Cu, and target skin distance 35–60 cm. Finally, we used the machine, the one still in use, which operates at 250 kv., filter 1.5 mm. Cu, half value layer 2.0 mm. Cu and target skin distance 35–50 cm. The longer target skin distance was frequently used in treating the more deeply seated tumors although the difference in depth dose at 50 cm. target skin distance compared to 35 cm. target skin distance is probably of little clinical value. For example, through a 4 cm. cone the depth dose at 5 cm. with a target skin distance of 50 cm. per 100 r in air is about 55 r. When the target skin distance is changed to 35 cm., the dose at 5 cm. is 50 r and the treatment time is halved.

One interesting and important clinical observation was made by us during these years. As the potential of our roentgen-ray machines was increased from 200 kv. to 250 kv., the tissue reaction at the treatment site was less intense for the same air dose. It was necessary for us to increase the air dose 15 to 20 per cent to produce the same tissue reaction at 250 kv. which we were accustomed to see with the lower dose at 200 kv.

*Low Voltage Roentgen Rays.* We preferred low voltage peroral roentgen rays to treat superficially located cancers of the oral mucous membranes. The physical factors of our machine are 100–130 kv., filter none (except the tube wall, a 1.0 mm. Al equiv.) to a 0.1 mm. brass plus 0.25 mm. Al, half value layer 1.2–5.2 mm. Al and target skin distance 15–30 cm. The higher voltage, added filters and longer target skin distance were used for the more deeply infiltrating surface cancers. This machine is very flexible and can be easily adjusted to deliver accurately localized peroral treatment (Fig. 1). The rapid output at 100 kv.

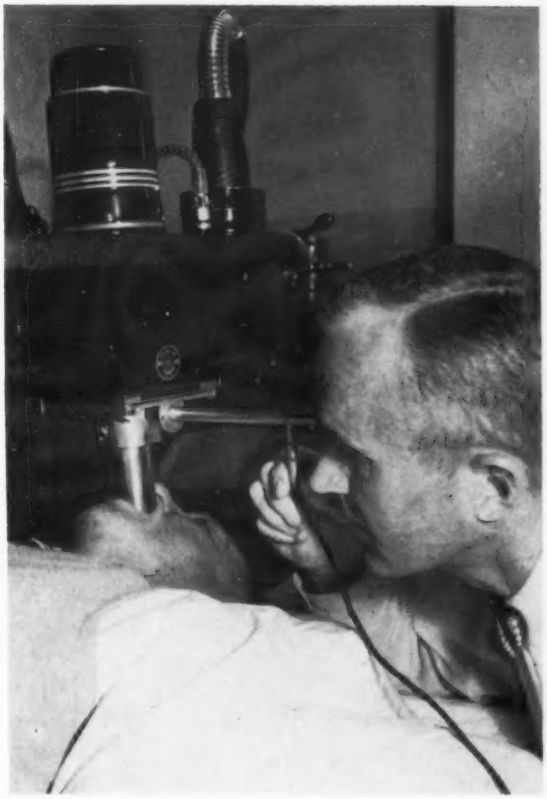
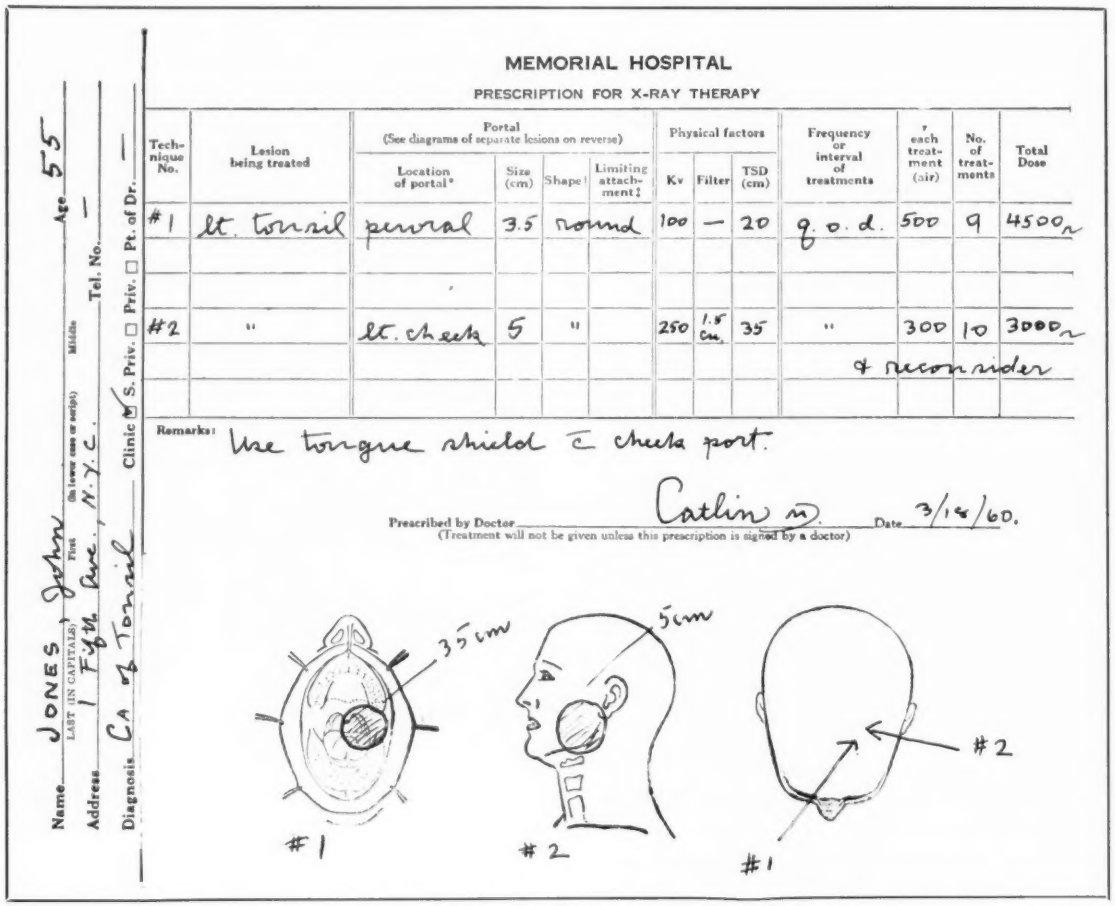


Fig. 1. Low voltage (100 kv.) roentgen therapy. The position of the peroral cylinder is checked by the therapist using an electrically lighted periscope.

with no added filter and at 20 cm. target skin distance (500 r in air in 2.4 minutes) enables a patient to remain perfectly quiet even during a somewhat uncomfortable peroral set-up.

*Position and Size of Port.* In contrast to some of the other physical factors of radiation therapy, the importance of portal position and size should be understood and can be carefully controlled. On our prescription form for radiation treatment, we indicate the ports, using anatomic diagrams to show their exact position and the direction in which the roentgen-ray beam is to be aimed (Fig. 2). Round or oval ports are employed almost exclusively to eliminate useless corners and thereby reduce the total volume of irradiated tissue by a significant amount (Fig. 3). We concentrate our effort on selecting the smallest port that will cover the cancer with a reasonable margin of surrounding normal appearing



MEMORIAL HOSPITAL

PRESCRIPTION FOR X-RAY THERAPY

Name JONES, John (In lower case or script) Middle — Age 55
Address 1 Fifth Ave., N.Y.C. Tel. No. —
Diagnosis Ca of Tonsil Clinic ☑ S. Priv. ☐ Priv. ☐ Pt. of Dr. —

| Technique No. | Lesion being treated | Portal (See diagrams of separate lesions on reverse) | | | | Physical factors | | | Frequency or interval of treatments | r each treatment (air) | No. of treatments | Total Dose |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Location of portal* | Size (cm) | Shape† | Limiting attachment‡ | Kv | Filter | TSD (cm) | | | | |
| #1 | lt. tonsil | peroral | 3.5 | round | | 100 | — | 20 | q.o.d. | 500 | 9 | 4500r |
| #2 | " | lt. cheek | 5 | " | | 250 | 1.5 Cu | 35 | " | 300 | 10 | 3000r |
| | | | | | | | | | & reconsider | | | |

Remarks: Use tongue shield & cheek port.

Prescribed by Doctor Catlin M.D. Date 3/18/60.
(Treatment will not be given unless this prescription is signed by a doctor)



FIG. 2. Roentgen-ray treatment prescription form listing treatment factors. Included also are anatomic diagrams showing the exact position of ports and the direction of the roentgen-ray beam.

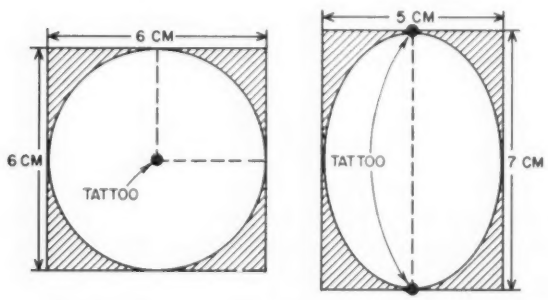



FIG. 3. Diagrams showing round and oval roentgen-ray ports. By eliminating useless corners the volume of tissue irradiated is reduced approximately 20 per cent. The tattoo marks are made in the skin and facilitate accurate placement of the port for each treatment (see text).

tissue. Two or more ports are employed whenever there is the possibility of cross firing the cancer. In this manner the total radiation dose through each port can be made less than if only a single port is used.

The position of the port is localized on the patient's skin by tattooing. A single tiny tattoo mark is used for a circular port. When two straight lines are drawn at a right angle on the skin from a central tattoo, the treatment cylinder can be perfectly centered by bisecting its circumference with both lines. For an oval port, two tattoo marks are made on the skin to correspond to the edges of the long diameter of the treatment area (Fig. 3). The use of these indelible cutaneous marks permits exact reproduction of the physical set-up day after day until the prescribed course of therapy is completed. In peroral roentgen treatment for accessible mouth cancers, the metal cylinder is accurately centered

over the lesion by visual inspection through an illuminated periscope incorporated into the machine (Fig. 1).

We feel strongly that the best way to destroy cancer is to keep the portal size as small as possible and run the total dose of roentgen rays up close to the limit of normal tissue tolerance. The smaller the port used, the larger the total dose of roentgen rays can be. In this entire study there were only 4 instances where cancer was controlled using a port of 10 cm. diameter or larger.

The use of small treatment ports necessitates the positioning of the patient under the roentgen-ray machine with great care and the prohibiting of motion during the treatment interval. Consequently we insist on contact between the machine and the patient. A metal cylinder (either round or oval) of selected diameter is pressed firmly against the skin (Fig. 4). Several small sandbags are used to help immobilize the head and neck.

All patients are examined frequently during treatment. If the radiation reaction does not appear properly localized, the size, position and direction of the treatment cylinder can be promptly corrected. Reliance on a moderate sized, accurately placed port based on a thorough knowledge of anatomy permits the administration of extremely well directed and effective radiation therapy.

*Roentgen-Ray Dosage.* Although the full importance of both protraction and intensity of roentgen rays is poorly understood, these factors are of practical value in planning a successful radiation dose. The prescription form is filled in carefully and the treatment is outlined to cover a period of three to four weeks (Fig. 2). Radiation treatments are given either daily or every other day, depending on the number of ports being used. Our patients are examined at frequent intervals between treatment "set-ups." The treatment program can be modified, interrupted, prolonged or completed, depending on the degree of tumor regression, the intensity of the radiation reaction and the tolerance of the patient. The daily and total doses of radiation given to each port have been worked out by trial and error plus a good deal of hard experience. The details of treatment and the dosage data are included in the section on Radiation Treatment Techniques further along in this report.

Fig. 4. High voltage (250 kv.) roentgen-ray therapy. Note that the circular cylinder is pressed firmly against the patient's neck to prevent any motion during the treatment period.

The output of our roentgen-ray machines is measured in roentgens delivered in air. Our daily and total doses to each treatment port are expressed also in roentgens in air. The "air" dose is fundamental. It can be easily and accurately measured; it is the basic "applicator" dose from which all other kinds of doses must be derived. Our radiation and physics departments have taken our air doses and from them calculated tissue doses in the various tumors at the center of the roentgen-ray beam. To

complete our treatment record, these central tissue doses are listed adjacent to our air doses in the section under Radiation Treatment Techniques.* Knowing our own inability to determine with any degree of accuracy either the exact position or extent of any given cancer, we place little confidence in the value of a "calculated" tissue dose.

### RADON SEED THERAPY

Since 1926 there has been available at Memorial Hospital an apparatus for collecting the radon gas emanating from a solution of radium chloride, the so-called Radium Emanation Plant. Radon gas is pumped into fine gold tubing which is cut and sealed in 4.0 mm. lengths to form our "radon seeds." These seeds vary in radioactive strength from 0.3-3.0 mc. The 0.3 mm. wall thickness of the gold tubing removes by filtration 91 per cent of the beta radiation given off by the radon. The half life of a radon seed is 3.82 days, making it unnecessary to remove it from the tissue into which it is implanted.

*Interstitial Radon Implantation.* Gold radon seeds are considered by us to be most useful and practical for supplementing roentgen therapy with interstitial radiation. Our practice is to insert seeds whenever possible and not to rely exclusively on roentgen rays to destroy the cancer being treated. We plan to interrupt roentgen treatment about one-half way through the prescribed course and implant the cancer with radon seeds. Following a rest of two to three days roentgen treatment is resumed and, when completed, a second dose of seeds is implanted if any palpable tumor remains. In a few instances even a third dose of seeds may be needed one week later if the cancer has failed to regress completely. In the early years of this study we used seeds containing 1.5–2.0 mc each and frequently implanted a total amount of 30–40 mc.

Further experience taught us that we could avoid or at least minimize tissue necrosis by using seeds of the strength of 1.0 mc or less and by never implanting more than 20–30 mc in any one area of the mouth or neck.

*Radon Seed Dosage.* The dose of gold seeds is best expressed as the total number of millicuries implanted. This again (as with r in air for roentgen rays) is the basic "applicator" dose from which all other doses must be calculated. The millicurie hour dose is obtained by multiplying the total millicuries implanted by 133 hours. An approximate tissue dose can be calculated by estimating the volume of tissue implanted and assuming that the seeds have been uniformly distributed in the treated area. Such tissue doses have been calculated for the seeds by our Radiation Physics Department and are included in the section on Radiation Treatment Techniques. Clinically, we prefer to rely on the dose of millicuries implanted.

*Technique of Radon Seed Implantation.* The implantation of gold seeds is not difficult and with care a reasonable, although not perfectly uniform, distribution of sources can be obtained. With a local infiltration of novocain, a trocar is used to carry the seed through a puncture wound in healthy skin into the cancer, thus avoiding direct trauma to an ulcerated and superficially infected tumor. Intravenous pentothal is occasionally used when implanting a tender, painful cancer in the mouth or pharynx. Cancers of the tongue, floor of the mouth, and tonsil lend themselves well to implantation through the skin of the upper neck (see diagram in section on Radiation Technique for Cancer of the Floor of the Mouth). Metastatic neck lymph nodes are implanted directly through the overlying normal skin (see diagram in section on Radiation Technique for Cancerous Neck Lymph Nodes). We try as nearly as possible to implant the seeds 1.0 cm. apart; perfect distribution is impossible, but a good spacing of seeds is facilitated in those cases in which no trocar is removed until the whole implantation is completed. Despite this somewhat crude and empirical method of using interstitial radiation, the

* The author wishes to express his appreciation to Mr. Richard F. Nelson and Dr. John Laughlin of the Physics Department for the dosimetry analysis of the external radiation and of the interstitial radon applicators.

clinical effect is often most gratifying; it has aided on many occasions in the permanent destruction of deposits of cancer.

*Nasopharyngeal Radon Seed Applicator.* In treating cancers of the nasopharynx, the use of interstitial radiation is impractical because most of these tumors are too small to be implanted with radon seeds. Consequently, we use a small brass applicator (filtration: 2.2 mm. brass equiv.) containing radon seeds which is inserted through the nasal cavity so as to rest adjacent to the cancer (see diagram in section on Radiation Technique for Cancer of the Nasopharynx). The brass capsule on the applicator is loaded with 12–14 mc of radon sufficient to give a dose of 500–600 mc hr. in forty-eight hours. In this type of intracavitary radiation, the dose must be expressed in millicurie hours and not in millicuries implanted as the applicator is removed after a specified interval. It is our practice to insert the nasopharyngeal applicator one-half way through the course of roentgen-ray treatment.

A technique of radiation therapy using a combination of roentgen rays and radon seeds makes it possible to keep our treatments within the range of previous successes without being forced to use the maximum amount of either agent. Such a program seems to us both reasonable and practical.

## RADIATION TREATMENT TECHNIQUES

In this section nine different techniques are given for treating nine different anatomic forms of mouth, pharynx, larynx, and neck cancer. Not all of the successful cases included in this report were treated only by the nine techniques described. Some of the earlier cases were treated with different roentgen-ray machines and with some modifications in the other treatment factors.*

Despite frequent minor variations, the basic principles of our treatment have remained the same. The techniques described here are the ones in current use on our Head and Neck Service and seem to be the most satisfactory to date. No originality or infallibility is claimed for these techniques; they are simply the treatment methods which have been most often successful in our hands.

In describing these treatments the adjectives "median" and "range" are purposely used to modify the size of the lesions and roentgen-ray ports, all the doses, and the length of therapy. The *median figure* is one around which the greatest number of successes was found. The *range figures* denote the limits in variation in size and other factors within which all our successful cases lay. The median figure coupled with its range of successful values is more accurate and informative than a single average figure. Almost no controlled cases were found outside the ranges listed; those which were, are too bizarre for useful analysis. Attention is directed to the very broad range in doses in most of our techniques. This is best explained by the marked variation with which supposedly similar cancers respond to identical forms of radiation treatment. One cancer will completely regress with a dose of "X" roentgens; a second, similar appearing cancer will show only a moderate degree of regression following a dose of "2 X" roentgens, and so forth. Little is yet understood about this biologic difference in cancers.

In general, it can be stated that, in most instances where the portal size is small, the total dose of roentgen rays will lie at the high end of the range. Conversely, when the port is large, the roentgen-ray dose tends to be at the low end of the range. Also the total dose of roentgen rays is usually influenced by the amount of interstitial radon seeds used; the greater the number of seeds implanted, the nearer the lower end of the range is the total dose of roentgen rays and vice versa. The same can be said for the individual doses of roentgen rays, which also tend to vary inversely with different portal sizes; the lower doses are coupled with the larger ports and vice

* Those readers interested in examining our other treatment techniques are referred to the manual "Treatment Factors in Radiation Therapy of Cancer of the Mouth, Pharynx and Larynx" by Hayes Martin, M.D. Published by United Surgical Supplies Co., Mamaroneck, New York, 1954.

versa. The length of the treatment period is largely governed by the number of ports used and individual set-ups needed to complete the outlined course. Those cases which require multiple ports are under treatment the longest (for more about protraction of treatment see Discussion section).

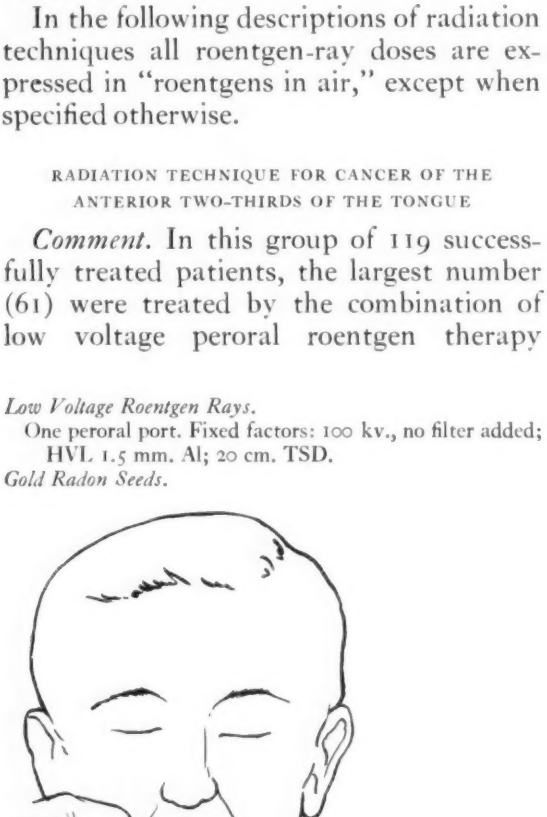
All the above mentioned facts become increasingly self evident with practice. The important thing to remember in treating new cases is to approximate these *mean* doses when feasible and always be doubly certain that the program of treatment is so planned as to lie within the *range* of previous success.

In the following descriptions of radiation techniques all roentgen-ray doses are expressed in "roentgens in air," except when specified otherwise.

### RADIATION TECHNIQUE FOR CANCER OF THE ANTERIOR TWO-THIRDS OF THE TONGUE

*Comment.* In this group of 119 successfully treated patients, the largest number (61) were treated by the combination of low voltage peroral roentgen therapy supplemented with gold radon seeds. We favor the low voltage apparatus for peroral set-ups because of its extreme flexibility and the accuracy with which the treatment cylinder can be centered on the cancer. Radon seeds are implanted either directly into the tongue cancer or preferably through the skin of the submental area when possible; they augment the depth dose around and within the cancer. In most of these patients the radon seeds were implanted in a single dose or in two doses divided by a seven to ten day interval during the course of peroral roentgen irradiation. The larger doses of radon were given in association with the lower total doses of roentgen rays. In 9 patients no radon seeds were used at all because of rapid and complete regression of their tumors with roentgen rays alone. One 8 cm. tumor was actually 8×3.5 cm. and the largest practical cylinder (4 cm.) was used tangentially, thereby covering the whole diameter of the cancer. In recent years we have preferred surgery for cancers located in the anterior two-thirds of the tongue.

*Low Voltage Roentgen Rays.*
One peroral port. Fixed factors: 100 kv., no filter added; HVL 1.5 mm. Al; 20 cm. TSD.
*Gold Radon Seeds.*

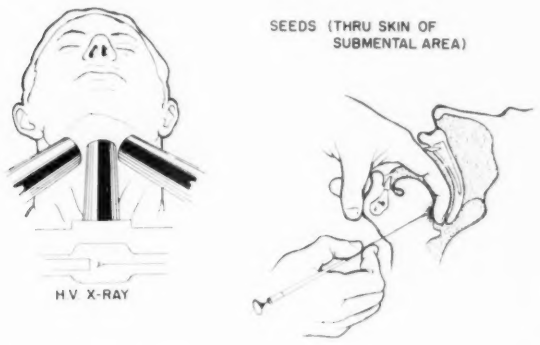



### RADIATION TECHNIQUE FOR CANCER OF THE BASE OF THE TONGUE

*Comment.* Thirty-two of these 55 patients were treated with two lateral ports only, the third suprahyoid port being omitted. The median total dose of roentgen rays and the successful range doses using two lateral ports are: total dose: median 3,800 r×2 (range 2,100 r×2–6,600 r×2). In our more recent cases we have added the third port, our purpose being to reduce

*Size of Tongue Cancer.*
Median diameter 2 cm. (range 1–8 cm.)
*Roentgen Therapy.*
*Peroral Port:* Median diameter 3 cm. (range 2–5 cm.)
Individual Dose: Median 600 r (range 350–1,000 r)
Total Dose: Median 10,000 r (range 3,000–12,000 r) (tumor dose: 6,600 r)
*Radon Seeds.*
Total Dose: Median 9 mc (range 4–25 mc) (tumor dose: 10,000 r)
*Treatment Period.*
Duration: Median 30 days (range 12–58 days)

*High Voltage Roentgen Rays.*
Two lateral ports, one suprahyoid port. Fixed factors: 250 kv.; HVL 2.0 mm. Cu; 35 cm. TSD.
*Gold Radon Seeds.*




*Size of Tongue Cancer.*
Median diameter 3 cm. (range 1–7 cm.)
*Roentgen Therapy.*
*Lateral Ports:* Median diameter 6 cm. (range 6–7 cm.)
*Suprahyoid Port:* Median diameter 5 cm. (range 5–7 cm.)
Individual Dose: Median 400 r (range 250–400 r)
Total Dose: Median 3,500 r × 3 (range 3,000 r × 3–4,200 r × 3) (tumor dose: 5,000 r)
*Radon Seeds.*
Total Dose: Median 23 mc (range 6–35 mc) (tumor dose: 8,000 r)
*Treatment Period.*
Duration: Median 36 days (range 24–64 days)

slightly the total roentgen-ray dose through each port while maintaining the same or an increased dose to the base of the tongue. The largest base of tongue cancer controlled by radiation was 7 cm. in diameter and was an isolated instance. Large cancers in this area are now attacked surgically, particularly if a metastatic neck lymph node (or nodes) is present on the first examination.

### RADIATION TECHNIQUE FOR CANCEROUS (METASTATIC) NECK LYMPH NODES

*Comment.* During the first ten years or so of this report, the treatment of cervical metastatic cancer was almost exclusively by some form of roentgen therapy. In most instances we employed a single high voltage neck port supplemented with interstitial seeds as outlined in the preceding paragraph. The seeds were usually implanted one-half way through the treatment program with a possibility of a second implantation at the completion of roentgen irradiation if residual cancer was palpable. In a few patients even a third implantation was done. Our tendency was to match the smaller dose of roentgen rays with the larger dose of radon and vice versa. In 10 patients in this group of 113 cases, no radon seeds were used as regression was complete without them. We learned that the single most important factor in controlling neck cancer by radiation was the size of the growth. The smaller the area of metastasis, the better the prognosis. Roentgen-ray ports larger than 8 cm. in diameter were only rarely successful. Larger ports of 10, 11, and 14 cm. were each successful in 1 patient only; a 12 cm. port controlled neck cancer in 2 instances. This serious limitation of effective irradiation to the neck has convinced us that complete neck dissection is the treatment of choice in most of the resectable cases.

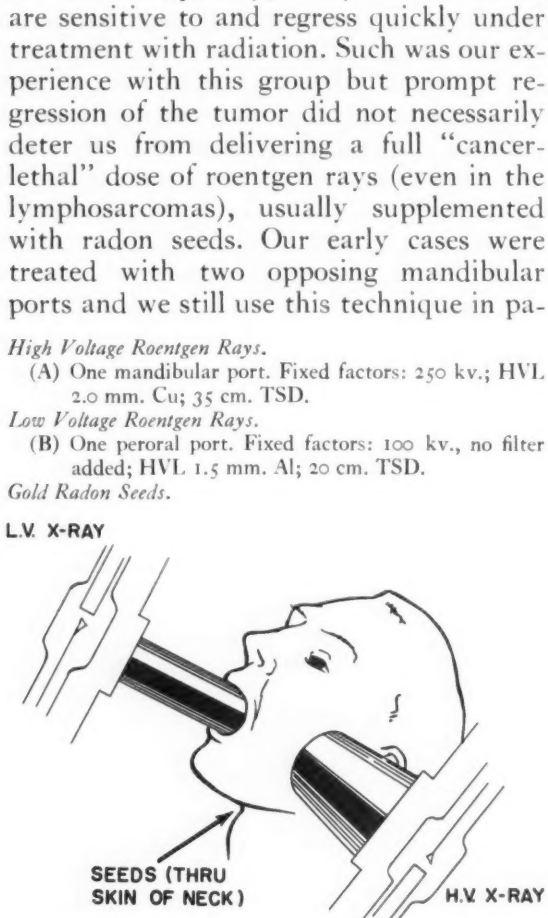
*High Voltage Roentgen Rays.*
One neck port. Fixed factors: 250 kv.; HVL 2.0 mm. Cu; 35 cm. TSD.
*Gold Radon Seeds.*

*Size of Neck Cancer.*
Median diameter 3 cm. (range 1–9 cm.)
*Roentgen Therapy.*
*Neck Ports:* Median diameter 4 cm. (range 2.5–14 cm.)
Individual Dose: Median 400 r (range 150–1,000 r)
Total Dose: Median 5,000 r (range 3,000–10,000 r) (tumor dose: 3,650 r)
*Radon Seeds.*
Total Dose: Median 17 mc (range 3.5–27 mc) (tumor dose: 15,000 r)
*Treatment Period.*
Duration: Median 27 days (range 12–53 days)

RADIATION TECHNIQUE FOR CANCER OF THE TONSIL

*Comment.* Cancers of the tonsil are frequently undifferentiated and anaplastic. In addition, the tonsil is the most common site in the mouth and pharynx for lymphosarcoma. Consequently, many tonsil cancers are sensitive to and regress quickly under treatment with radiation. Such was our experience with this group but prompt regression of the tumor did not necessarily deter us from delivering a full "cancer-lethal" dose of roentgen rays (even in the lymphosarcomas), usually supplemented with radon seeds. Our early cases were treated with two opposing mandibular ports and we still use this technique in patients in whom peroral therapy is not practical. The roentgen-ray doses for the two high voltage mandibular ports are as follows: total dose: median 4,100 r×2 (range 2,200 r×2–4,500 r×2). During the last few years we have been performing radical operations on many patients with tonsil cancers who also present homolateral metastatic lymph nodes on the first examination.

*High Voltage Roentgen Rays.*
(A) One mandibular port. Fixed factors: 250 kv.; HVL 2.0 mm. Cu; 35 cm. TSD.
*Low Voltage Roentgen Rays.*
(B) One peroral port. Fixed factors: 100 kv., no filter added; HVL 1.5 mm. Al; 20 cm. TSD.
*Gold Radon Seeds.*

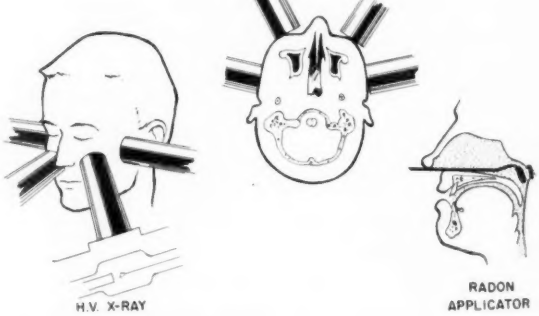



*Size of Tonsil Cancer.*
Median diameter 3 cm. (range 1–6 cm.)
*Roentgen Therapy.*
(A) *Mandibular Port:* Median diameter 5 cm. (range 4–7 cm.)
Individual Dose: Median 350 r (range 300–600 r)
Total Dose: Median 4,000 r (range 3,000–6,300 r) (tumor dose: 2,280 r)
(B) *Peroral Port:* Median diameter 3.5 cm. (range 2.5–4.5 cm.)
Individual Dose: Median 500 r (range 400–1,000 r)
Total Dose: Median 7,000 r (range 2,500–9,000 r) (tumor dose: 4,760 r)
*Radon Seeds.*
Total Dose: Median 9 mc (range 3–25 mc) (tumor dose: 10,000 r)
*Treatment Period.*
Duration: Median 28 days (range 17–50 days)

RADIATION TECHNIQUE FOR CANCER OF THE NASOPHARYNX

*Comment.* Although cancers of the nasopharynx are usually small (the largest in our group was 3 cm.), their deep location and intimate contact with the base of the skull will undoubtedly preclude their successful removal by surgery. All our cases were treated by radiation and in the beginning we used only two cheek ports. Somewhat later we added the nasopharyngeal radon applicator and then a third high voltage peroral port. A high incidence of radionecrosis of the soft palate discouraged

*High Voltage Roentgen Rays.*
Two malar ports; two zygomatic ports. Fixed factors: 250 kv.; HVL 2.0 mm. Cu; 35 cm. TSD.
*Intracavitary Radon Applicator.*




*Size of Nasopharynx Cancer.*
Median diameter 2 cm. (range 0.5–3 cm.)
*Roentgen Therapy.*
*Malar and Zygomatic Ports:* Median diameter 5 cm. (range 4–6 cm.)
Individual Dose: Median 400 r (range 200–600 r)
Total Dose: Median 3,500 r × 4 (range 2,100 r × 4–4,100 r × 4) (tumor dose: 5,500 r)
*Radon Applicator.*
Total Dose: Median 600 mc hr. (range 500–1,600 mc hr.) (tumor dose: 15,000 r)
*Treatment Period.*
Duration: Median 36 days (range 20–58 days)

continued use of a peroral cylinder. Finally we adopted the technique of four cheek ports supplemented with the radon capsule which remains our treatment of choice now. We cross fire the nasopharynx with multiple ports and avoid giving an excessive dose of roentgen rays through any single port.

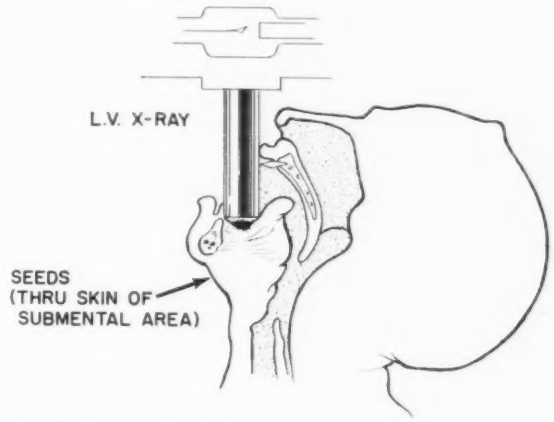
It is customary to insert the radon applicator into the nasopharynx at a stage halfway through the treatment period, at which time the roentgen irradiation is interrupted for four to five days. The applicator remains in the nasopharynx for forty-eight hours. Our early doses of radon were large (approximately 1,000–1,200 mc hr. and in 1 patient 1,600 mc hr.) and, though successful, were frequently followed by persistent radionecrosis and exposed bone. We have learned that the most satisfactory dose for intracavitary radon is 500–700 mc hr.

Most of our patients with nasopharynx cancer also have metastasis to the neck lymph nodes, frequently bilaterally. The nasopharynx cancer is usually destroyed by our irradiation but failure to cure is due to uncontrolled regional or systemic metastasis.

### RADIATION TECHNIQUE FOR CANCER OF THE FLOOR OF THE MOUTH

*Comment.* Radiation treatment of cancer of the floor of the mouth has been most successful in small and centrally located tumors when the adjacent alveolar ridge and mandible could be adequately protected from the destructive effect of cancer-lethal irradiation. In this present series of 51 cases, the largest successfully treated cancer was 6 cm. in diameter; in this case an additional 4,500 r of roentgen rays (200 kv.) was given through a 7 cm. submental port. For most of our patients, we favored the use of a single low voltage peroral port supplemented with radon seeds. The set-up was sometimes difficult and required extraction of some anterior teeth to permit accurate angulation of the peroral cone. Both circular and oval ports were used, care being taken to protect the adjacent alveolar ridge. For this purpose special lead shields were made by our dental department to accurately fit over the lower gum. Radon seeds were implanted through the skin of the submental area with a guiding finger placed on the cancer in the floor of the mouth. Irradiation of more extensive cancers resulted in so much prolonged radionecrosis of the mandible that surgery is now preferred for these larger tumors.

*Low Voltage Roentgen Rays.*
One peroral port. Fixed factors: 100 kv., no filter added; HVL 1.5 mm. Al; 20 cm. TSD.
*Gold Radon Seeds.*




*Size of Floor of Mouth Cancer.*
Median diameter 2 cm. (range 1–6 cm.)
*Roentgen Therapy.*
*Peroral Port:* Median diameter 3 cm. (range 2–5 cm.)
Individual Dose: Median 500 r (range 400–1,000 r)
Total Dose: Median 9,500 r (range 6,000–12,000 r) (tumor dose: 6,270 r)
*Radon Seeds.*
Total Dose: Median 8 mc (range 5–22 mc) (tumor dose: 9,000 r)
*Treatment Period.*
Duration: Median 25 days (range 18–35 days)

### RADIATION TECHNIQUE FOR CANCER OF THE EXTRINSIC LARYNX

*Comment.* From 1931 until about 1944 all our patients with extrinsic larynx cancer were treated with some form of radiation. In some of the early cases we tried supplementing roentgen rays with radon seeds, which we either implanted into or placed on the surface of the cancer with an applicator. Following the use of radon seeds, there were frequent complications due to

*High Voltage Roentgen Rays.*
Two oblique ports. Fixed factors: 250 kv.; HVL 2.0 mm. Cu; 50 cm. TSD.

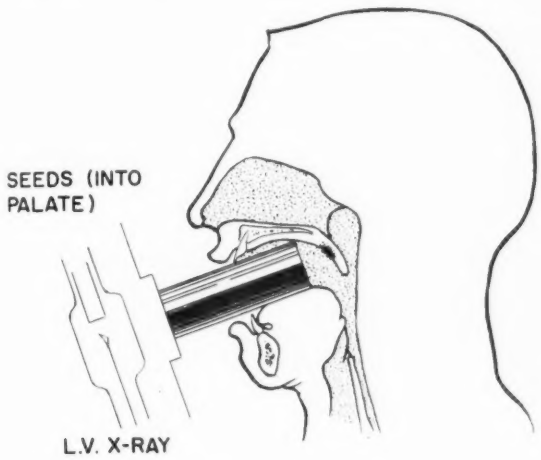
*Size of Extrinsic Larynx Cancer.*
Median diameter 2.5 cm. (range 1–4 cm.)
*Roentgen Therapy.*
*Oblique Ports:* Median diameter 7 cm. (range 5–10 cm.)
Individual Dose: Median 350 r (range 150–500 r)
Total Dose: Median 4,000 r × 2 (range 3,500 r × 2–5,100 r × 2) (tumor dose: 6,000 r)
*Treatment Period.*
Duration: Median 31 days (range 13–52 days)

slough and necrosis occurring in the larynx. There were very few successes and the radon seeds were soon abandoned. There remains only 1 five year control in which supplementary radon seeds were used in the extrinsic larynx. Radionecrosis in the larynx was a serious complication, usually resulting in failure; there were only 2 such patients in a total of 50 successful cases. As a matter of some interest a careful study was made of 100 cases of extrinsic larynx cancer in which roentgen therapy failed to cure. Larynx cancer was chosen purposely because the roentgen treatment is simple and direct; no radon seeds were used. Only those cases were selected in which the prescribed course of treatment was completed as outlined. Failure was due either to persistent cancer in the larynx or to the lethal effects of radiation such as radionecrosis, hemorrhage and sepsis. Patients with advanced larynx cancer and those who did not complete treatment were excluded from this study. Among the failures, the primary tumors were similar in size and extent to those seen in the 50 successfully irradiated cases. The treatment factors, the median dose, and dosage range were similar for both groups. Successes and failures fell into the same general treatment pattern. In about one-half of the failures, radionecrosis and persistent cancer were coexistent on the same site; a roentgen ray dose sufficient to kill normal tissue was inadequate to destroy cancer. The only reasonable explanation for the difference between success and failure is to assume that some cancers are curable by roentgen rays and others simply are not, regardless of the dose and physical factors used. We finally came to rely entirely on high voltage roentgen rays (200–250 kv.) delivered through oblique circular ports, so directed as to cross fire the larynx. Today we use radiation only for nonresectable cases and for recurrence following surgery. Our preference for surgery as the initial form of treatment in all resectable extrinsic larynx cancers has greatly increased our over-all five year cure rate.

### RADIATION TECHNIQUE FOR CANCER OF THE SOFT PALATE

*Comment.* In this anatomic form of mouth cancer, we used at least 5 different radiation techniques, all of which were, on occasion, successful. Various combinations of external high voltage ports with or without a peroral low voltage port were all used, often supplemented with radon seeds. However, the technique which was most often successful and the one in greatest use now employs a single peroral roentgen-ray port supplemented with implantation of radon seeds. In 2 patients the soft palate cancers were 6 cm. in diameter and were too large to be covered by a peroral cylinder alone. Therefore, two lateral 7 cm. circular, high voltage cheek ports were added for a roentgen-ray dose of 3,000 r×2. A single small cancer of the soft palate was treated successfully with 10.1 mc of radon seeds alone. In most cases the seeds were implanted directly into the tumor through the

*Low Voltage Roentgen Rays.*
One peroral port. Fixed factors: 100 kv., no filter added; HVL 1.5 mm. Al; 20 cm. TSD.
*Gold Radon Seeds.*



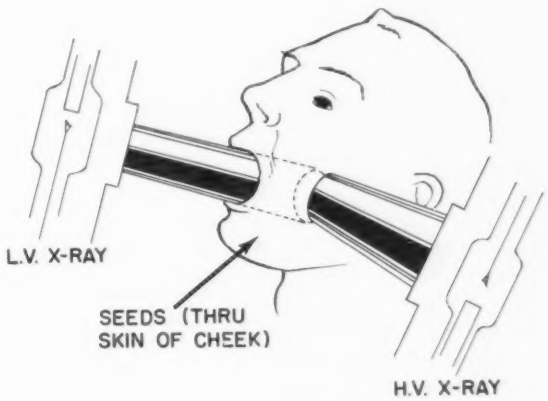

*Size of Soft Palate Cancer.*
Median diameter 2 cm. (range 1.5–6 cm.)
*Roentgen Therapy.*
*Peroral Port:* Median diameter 3 cm. (range 2.5–5 cm.)
Individual Dose: Median 500 r (range 400–800 r)
Total Dose: Median 8,500 r (range 6,000–11,000 r) (tumor dose: 5,600 r)
*Radon Seeds.*
Total dose: Median 6 mc (range 4–9 mc) (tumor dose: 8,000 r)
*Treatment Period.*
Duration: Median 25 days (range 16–31 days)

open mouth, usually at the halfway point in the roentgen treatment program. In 2 patients regression of the cancer was complete with roentgen rays and no radon seeds were used.

### RADIATION TECHNIQUE FOR CANCER OF THE CHEEK (BUCCAL MUCOSA)

*Comment.* Here again, roentgen irradiation proved successful mostly in small cancers which were located at a slight distance away from the maxilla and mandible. A single exception was a patient with a large (12 cm.) lymphosarcoma of the cheek which was successfully controlled with roentgen rays alone using a 12 cm. circular high voltage external port for a dose of 3,100 r. In the beginning, a single cheek port was used and the roentgen rays were supplemented with radon seeds. Later on, we added the second peroral port which is the preferred technique now. Radon seeds were used in a little more than one-half of our successful cases. Larger doses of radon were employed with the lower doses of roentgen rays. Implantation of the seeds was made through the skin of the cheek with a palpating finger placed on the underlying cancer. During treatment with the external cheek port, a lead shield was always placed in the mouth to protect the tongue from the roentgen rays. In our experience, irradiation of large cancers of the cheek has resulted in such a high incidence of painful osteoradionecrosis coupled with troublesome trismus that surgery is now preferred in almost all cases.

*High Voltage Roentgen Rays.*
(A) One cheek port. Fixed factors: 250 kv.; HVL 2.0 mm. Cu; 35 cm. TSD.
*Low Voltage Roentgen Rays.*
(B) One peroral port. Fixed factors: 100 kv., no filter added; HVL 1.5 mm. Al; 20 cm. TSD.
*Gold Radon Seeds.*




*Size of Cheek Cancer.*
Median diameter 3 cm. (range 1–12 cm.)
*Roentgen Therapy.*
(A) *Cheek Port:* Median diameter 6 cm. (range 2.5–12 cm.)
Individual Dose: Median 400 r (range 250–600 r)
Total Dose: Median 5,100 r (range 3,100–6,500 r) (tumor dose: 3,570 r)
(B) *Peroral Port:* Median diameter 3.5 cm. (range 2.5–4 cm.)
Individual Dose: Median 500 r (range 350–1,000 r)
Total Dose: Median 7,200 r (range 3,600–12,000 r) (tumor dose: 4,900 r)
*Radon Seeds.*
Total Dose: Median 7.5 mc (range 2–21 mc) (tumor dose: 8,500 r)
*Treatment Period.*
Duration: Median 25 days (range 15–64 days)

## DISCUSSION

Added to the careful study made of many hundreds of hospital records to collect this series of more than 600 successful irradiation cases are twenty years of personal experience in radiation treatment of patients with head and neck cancers. Over the same years there have been regularly scheduled conferences and numerous discussions concerning the management and many problems of radiation therapy among all the attending surgeons on our Head and Neck Service. From such an experience it would seem only natural to form certain impressions and observations on the whole subject. Although not strictly as factual as the reporting of our successful cases, the following comments are based directly on clinical experience and are not just intellectual whimsey.

### THE RADIATION REACTION

From the beginning of radiation therapy, clinical observation has revealed that it is necessary to produce an intense reaction in the treated tissues; the reaction must be sufficiently violent and prolonged to destroy the cancer while sparing the normal surrounding tissue. The process is somewhat similar to boiling an egg in water which is heated to 220° F. and held at that temperature for a selected time to cook the egg. To obtain the desired change in the egg it must be kept in the boiling water for a specified interval. The cooking period cannot be altered, interrupted or repeated later and still produce the same change in the egg. Similarly, in giving radiation therapy the tissues must be "heated up" (by ionization) and the reaction maintained until the desired effect (destruction) on the cancer is obtained. This concept helps in understanding why small doses of radiation with minimal tissue reaction are rarely successful and why a "course of irradiation" cannot usually be repeated with a successful outcome at a later date. Like egg boiling, irradiation of a cancer is a single planned operation and any modification of the dose must be made while the reaction is "hot." Unlike egg boiling, where the degree and effect of cooking are known, the exact amount of "heat" required to kill a cancer is unknown. Experience has indicated that we will most often succeed if we deliver the largest dose the normal tissues can tolerate and such has been our practice in most of our cases.

### FRACTIONATION (OR PROTRACTION) OF ROENTGEN-RAY TREATMENT

Ever since the first therapists discovered that tissue recovers at a fairly regular rate from the effect of radiation, the massive single dose technique of treatment was replaced by the multiple divided dose method. It was thought that not only could the total dose of roentgen rays be greatly increased by such protracted treatment, but also that the cancer cells could be exposed to ionization at a moment when they were extremely vulnerable (*i.e.*, during mitosis). On the basis of such conjecture, innumerable types of fractionation of the roentgen rays were tried and all sorts of advantages claimed. Despite this past furor of activity, the exact scientific value of protracted treatment remains obscure. Unfortunately, the differential in susceptibility to roentgen rays between cancer and normal tissue is not appreciably broadened by fractionating the total dose. Cancers, like normal tissue, also have a recovery rate.

However, there is a very practical reason (and probably the only good one) for fractionating roentgen treatment. If the exact dose needed to kill a cancer were known in advance, such a dose could be given at a single treatment without further ado. Alas, such a magic dose is never known with certainty at the start of treatment, so that we must fractionate our doses and "sneak up" on the final figure. Protraction gives us the chance to observe the response of the cancer to roentgen rays and to reserve decision as to the total dose until well along in the treatment program. A few more doses can be added to give the "coup de grâce" to the cancer or

the program may be cut short if the reaction warrants it. It is around the "end point" of treatment that the total dose range of our successful experience is so valuable. In brief, protraction of treatment is solely an empirical and practical aspect of roentgen therapy. It is employed to help the therapist arrive at an effective total dose and not for any mystically beneficial effect that it might have on either the cancer or the patient.

Due to the delay with which roentgen rays attain their full effect on tissue, about three to four weeks has proved to be a practical treatment period. The interval is longer when the treatment is complicated by the use of several ports or when there is a delay due to the implantation of radon seeds. Such planning has guided us in our performance on the successful cases reported here.

### ROENTGEN-RAY DOSAGE

Again, unfortunately, we have not found any magic dose of roentgen rays which can be relied upon with certainty to kill cancer. It is patently apparent that cancers differ in their susceptibility to roentgen rays. The various grades and types of cancer are so unreliable in their behavior that the value of any classification is limited. Since a reliable "tumor dose" is unknown, we did not try to use one in calculating the amount of treatment for our successful cases. We relied on the reaction produced by the "applicator dose" with the physical factors of the treatment set-up to determine the amount of radiation given in each case. The applicator dose is the actual amount of radiation given off by the apparatus used. It is an amount which can be simply and accurately measured. It is the basic dose from which all other types of doses must be calculated. The applicator dose for roentgen rays is expressed by roentgens in air, for radon seeds by millicuries implanted, and for the radon applicator by millicurie hours. When the applicator dose plus the physical factors of the treatment set-up are recorded, it is immediately apparent just how much radiation has been given. With such information a successful dose can be exactly repeated or intelligently modified as required. A tumor dose must be derived (often with considerable error) from the applicator dose and is simply an approximation of the number of roentgens or rads received by a tumor, the exact location and extent of which can only be guessed at. We do not think the total amount of radiation received by the cancer is as important as the *point dose* received by the one or two cancer cells which absorbed the least radiation. More important yet is the understanding that the calculation of any dose of radiation should be recorded with a complete statement of all the factors contained in the applicator dose. These respective factors can each vary widely and still by a proper combination produce the same "tumor dose." Often the radiologist or physicist calculates a tumor dose and omits a statement of these very factors. He simply states that the cancer received a certain number of roentgens or rads. Such a practice breeds confusion rather than clarity and simplicity.

Certainly, there is a place in the physics laboratory for the calculation of tissue doses in roentgens or rads. Such information may help in devising new and perhaps better ways of giving more effective radiation. In the meantime for the clinician the best measurement of radiation is still its effect on cancer.

### ROENTGEN-RAY PORTAL SIZE

The volume of tissue irradiated is without doubt the most important single factor in the successful radiation treatment of cancer. The tissue volume must be relatively small. For example, when cancer-lethal doses of roentgen rays are administered through 6–7 cm. circular ports, the patients remain comfortable and in good health for years provided no local complications supervene. When the ports are increased to 8, 9 or 10 cm. in diameter, the number of successful cases decreases so that very few patients are found free of cancer

for five years, and those who are, are not all functionally satisfactory (due to fibrosis of soft tissue, stomatitis sicca, trismus, radionecrosis, etc.). We know how important it is to use ports of small size carefully centered over the cancer. This knowledge is the basis for our insistence on round or oval ports—both shapes in which all useless corners are eliminated and in which the volume of tissue irradiated is reduced by more than 20 per cent over square and rectangular ports of similar dimensions. Our disappointing experience with large ports has impressed upon us the futility of irradiating one whole side of the neck for metastatic cancer. We prefer neck dissection and reserve radiation for smaller well localized deposits of cancer. We have read many articles on therapy where the volume of tissue irradiated was not stressed or in many instances not even mentioned. In such reports it must be assumed that this vital factor was not sufficiently appreciated.

### PALLIATION WITH ROENTGEN RAYS

There is still considerable confusion as to just what is meant by the term, palliative roentgen-ray treatment. How much treatment, to what area, for how long, palliates whom? For instance, we seriously question whether the use of roentgen-ray ports larger than 12 cm. is ever justified even in an effort to obtain palliation. Both the local and systemic dysfunction produced by even subcancer-lethal doses of roentgen rays given through large ports may be seriously harmful and sometimes rapidly fatal, proportionate, of course, to the dose administered. Better relief from the discomfort and pain of advanced cancer can often be secured by moderate doses of judiciously implanted weak radon seeds or by small doses of roentgen rays directed only to limited areas where the cancer is most active or painful.

### LATE COMPLICATIONS OF SUCCESSFUL RADIATION THERAPY

Some of the bitterest and most discouraging aspects of otherwise successful radiation therapy are the complications of treatment which appear years later and are often as lethal as the original cancer. Unfortunately, the destruction of cancer with roentgen rays produces a varying degree of damage to normal structures as well; such damage is not static and tends to become progressively worse. Some patients, who are apparently controlled, return eight or nine years later with new cancers growing at the margin of a previous treatment area in tissue damaged by radiation. These lesions are probably radiation induced cancers and their control by surgery is discouragingly difficult. Radical surgery made in any area of advanced radiation damage is fraught with danger and many complications are to be expected, some even fatal.

Many successfully irradiated mouth cancers develop late osteoradionecrosis requiring removal of large portions of the mandible or maxilla, often more disfiguring and disabling than if the original treatment had been by surgery. Successfully controlled metastatic cancer in the neck is sometimes followed by late breakdown of the irradiated tissues, with exposure and then rupture of the carotid artery with all the danger inherent thereto. Radiation fibrosis in both sides of the neck has produced late bilateral vocal cord paralysis and dysphagia due to scarring around the vagus nerves. Such damage can convert the larynx into a useless and dangerous organ which must be removed to protect the patient from death by aspiration.

Experience with cases such as these tends to make one very thoughtful when deliberating the relative merits of radiation and surgery for the initial treatment of a new case.

### CONCLUSION

Our own experience indicates that we have not yet found the ideal combination of physical factors for the successful irradiation of the various forms of head and neck cancer. Radiation therapy, in general, over

the past twenty years has been an increasing disappointment to many of us who held high hopes for its ultimate possibilities. An example is the almost complete ineffectiveness of roentgen rays in controlling cancer which has invaded bone or lymph nodes. Consequently, we must continue to treat patients by radiation methods which we know have succeeded in the past. We must modify, refine and try to improve these techniques from time to time as new ideas and new equipment become available. We must give preference to surgery in those cases in which the morbidity can be decreased and the salvage increased over the results of radiation therapy described in this report.

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The author wishes to acknowledge his indebtedness to Dr. Hayes Martin, under whose direction this clinical material was collected and whose original idea it was to present our radiation experience in somewhat this fashion. Without his guidance and wisdom gained through many years of practice in the irradiation of head and neck cancers, and which he has so generously imparted to the author on innumerable occasions, it would have been most unlikely that this report would have been made.

# A STUDY OF RADIATION FAILURES AND THE ROLE OF RADIORESISTANCE IN THE TREATMENT OF CANCER OF THE CERVIX*

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DESPITE fifty years of radiation therapy for cancer of the cervix, an acceptable cancerocidal dose for this disease has not been defined. A dose simply expressed in units of radiation delivered in rads or roentgens is well known to be inadequate. This is because the biologic response of tissue to irradiation is dependent on much more than the total roentgens delivered. A variety of factors are known to influence this biologic response and have been described. Many others are still unknown.

The many factors now recognized to influence the biologic response may be divided into two groups. One group includes those traits which are inherent or dependent on the tumor itself. The second group consists of those factors associated with the administered therapy. The former group is represented by such entities as the gross microscopic characteristics of the tumor, presence or absence of infection, mitotic rate, blood supply, and oxygen tension within the tumor. This is not intended to be a complete list, for at present many more are known and more are apt to be added in the near future. But, for the purposes of this presentation, these will suffice to denote the aspects to which we allude. Probably the most important factor of the second group is the intensity of irradiation, or the time-dose relationship, and this includes fractionation and protraction.

Modification in any one of the aforementioned features is capable of influencing the biologic response of a specific tumor, all other factors remaining equal. The experienced radiotherapist has learned to take advantage of this characteristic and under certain conditions, or in the presence of certain of these features, will modify and alter the time dose relationship to obtain optimal results. At present this qualification is an empirical one for there is no way of totaling the individual agents present in any one situation in such a way as to allow the prescription of a minimal dose and time factors which will guarantee the eradication of a tumor. There is no formula which equates all the features of the tumor to the therapy factors, nor are there any specific rules which will allow compliance for the changes.

Observation of many cases, however, has led to certain determinations which, in general, are the physical measurements seemingly necessary to control cancer and the definition of a range of dosage within which the majority of the cases fall. As an example, Strandqvist[10] has plotted a curve which does just this for carcinoma of the skin. The data were assembled many years ago and relate only to squamous cell carcinoma of the skin. There has not been any comparable study for carcinoma of the cervix. Neither has there been any demonstration of the validity of this curve for carcinoma of the cervix. Nevertheless, because of the fragmentary evidence of its analogous value in relation to cervical cancer, coupled with the lack of anything better, it has come to be generally accepted as satisfactory. A comparable study of this nature for carcinoma of the cervix is of the utmost importance and a necessity at the present time.

In the mechanics of treatment for cervi-

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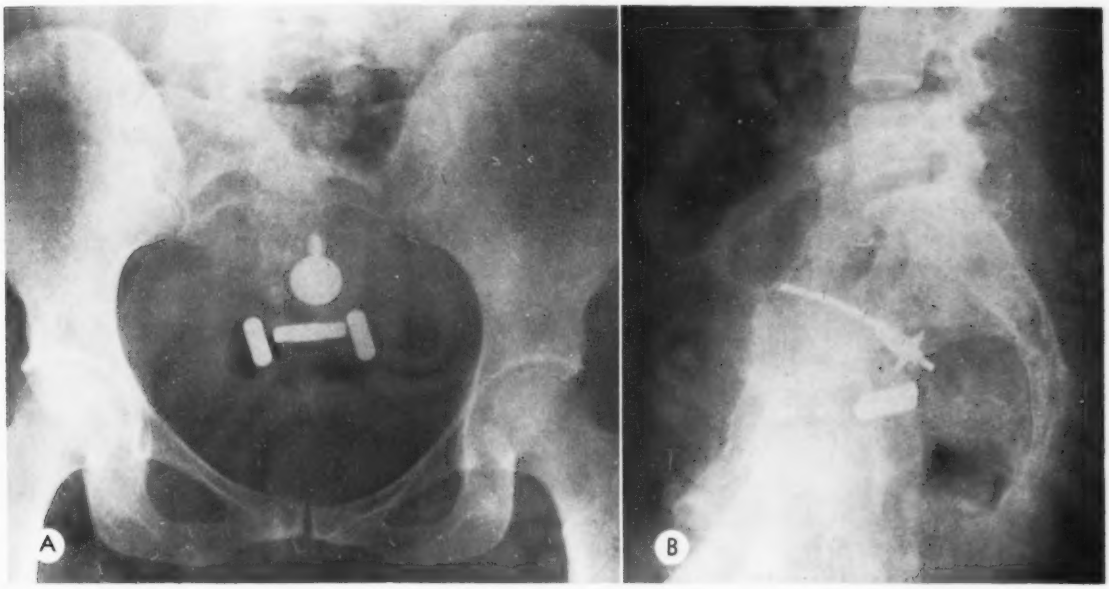


Fig. 1. (*A* and *B*) Case I.

cal carcinoma, an attempt is made to deliver at the minimum a cancerocidal dose to the cervix. In actual practice because of the endeavor to increase the dose to the lateral areas of the pelvis, a dose much in excess of an acceptable cancerocidal dose is administered to the cervix and adjacent vagina. A safe dose for this area would be a tolerance dose to the rectum, bladder and point A as described by Tod and Meredith.[11,12] In summary, therefore, an attempt is made to deliver a maximum dose to the pelvic structures within their tolerance, and, in so doing, it is reasonable to expect that the cervix and adjacent vagina will receive a dose in excess of the cancerocidal dose. As an outcome of such practice and reasoning, it has been accepted that a satisfactory dose to the cervix would be supplied by the use of radium applied in the form of a uterine tandem and vaginal ovoids over a period of four to five weeks and in one to three applications for 5,000 to 8,000 mg. hr. (depending on the type of colpostat used). Although we recognize the wide range of biologic responsiveness due

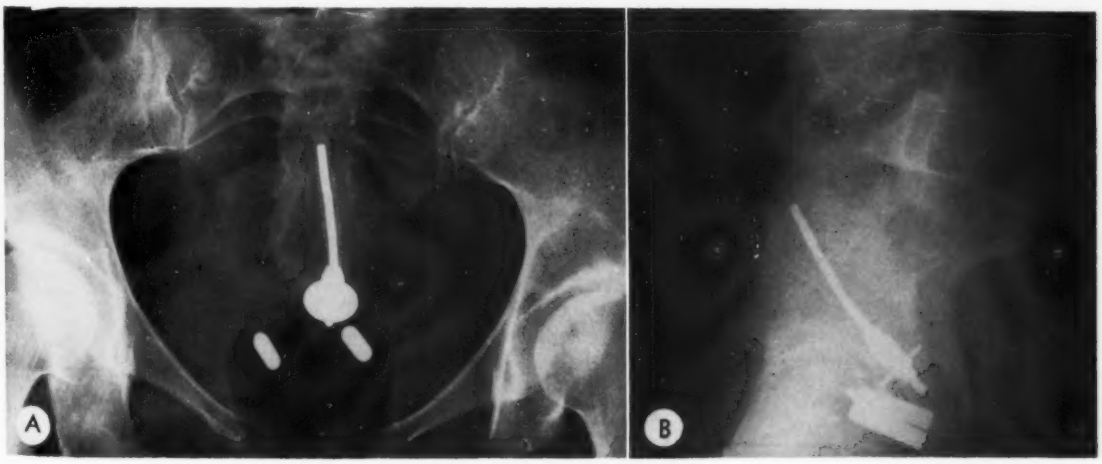


Fig. 2. (*A* and *B*) Case II.

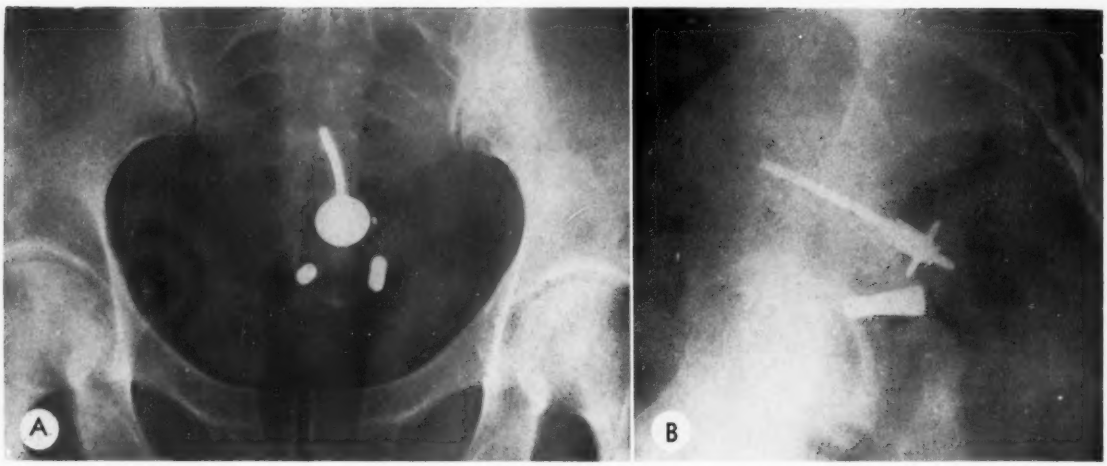


Fig. 3. (*A* and *B*) Case III.

to different factors, both in the tumor and the applied therapy, there is a generalized therapy dose which should encompass these variables and yield successful results.

The eradication of a cancer of the cervix by irradiation implies that a dose was delivered to all tumor bearing areas of sufficient magnitude and intensity to cause directly, or indirectly, the destruction of the cancer. Conversely, therefore, it may be said that failure to obtain such eradication implies that the necessary dose was not delivered.

A physical feature of radiation is that the intensity varies inversely with the distance from the source. Because of the anatomy of the pelvis and the direction of spread of the cancer laterally within this anatomic framework, there are areas in the lateral parts of the pelvis which are relatively removed from the radium sources. Staying within the confines of tolerance dosages allows for the fact that there will be areas in the lateral parts of the pelvis which fall beyond the effective range of irradiation. Therefore, it may be argued logically that the failure to eradicate cancer in the lateral parts of the pelvis is directly due to the inability in certain cases to deliver adequate cancerocidal doses of radiation as defined above. This has been borne out by many studies[8] in

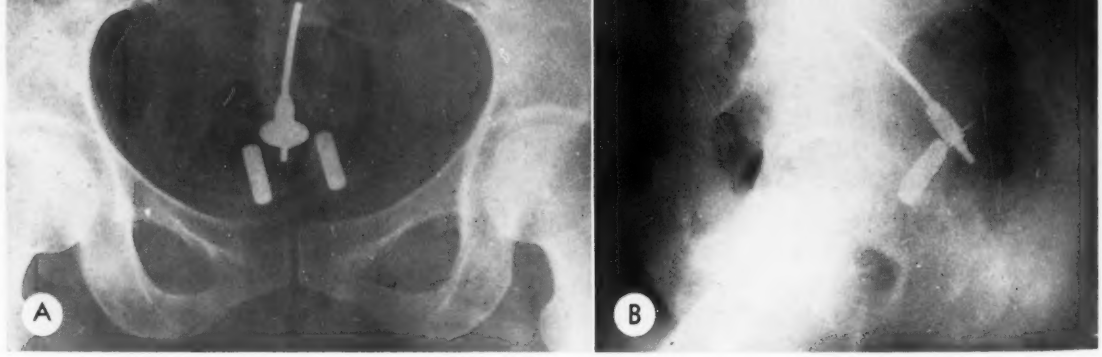


Fig. 4. (*A* and *B*) Case V.

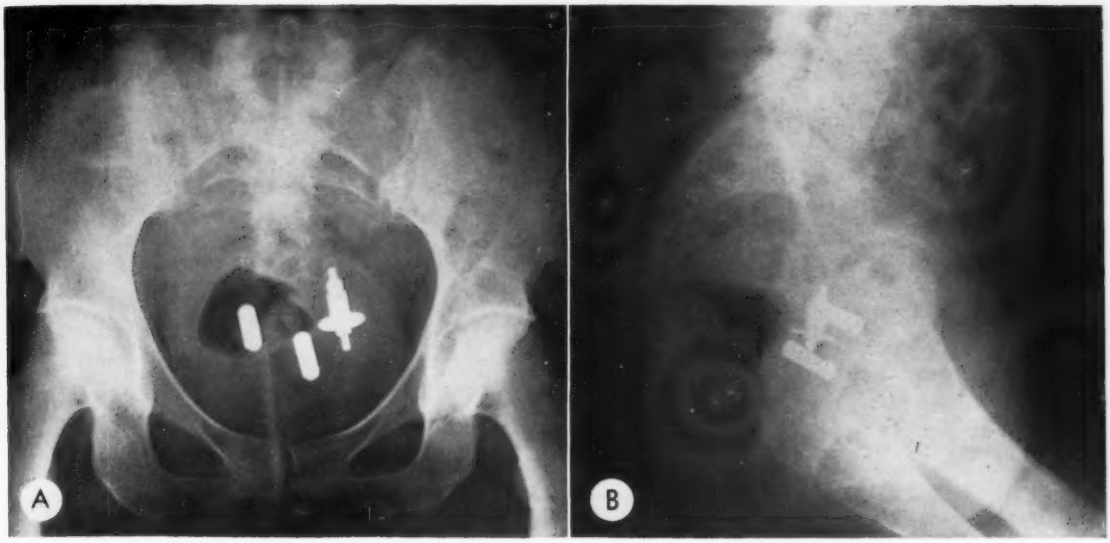


Fig. 5. (*A* and *B*) Case vi.

which attempts were made to measure the total doses delivered to the parametria.

However, the primary site of the cancer at the cervix and within its immediate periphery is so readily accessible to the radium that it would be extremely rare to anticipate an inability to deliver to the cervix a dose of radiation within the wide scope of the acceptable range. It is this very notion which probably accounts for the factor known as radioresistance of cervical cancer. The unexplained persistence of a cervical cancer after its irradiation with an adequate dose and by a method which should prove successful is why such cancers are quite apt to be labelled "radioresistant." This is substantiated by the frequency with which the term appears in the recent literature dealing with cervical cancer, and for this reason there has been an impetus in the resurge of surgical procedures for these cases. By the same token great furor in the search for techniques and means by which to define and diagnose the presence of cervical cancer prior to treatment by irradiation has been

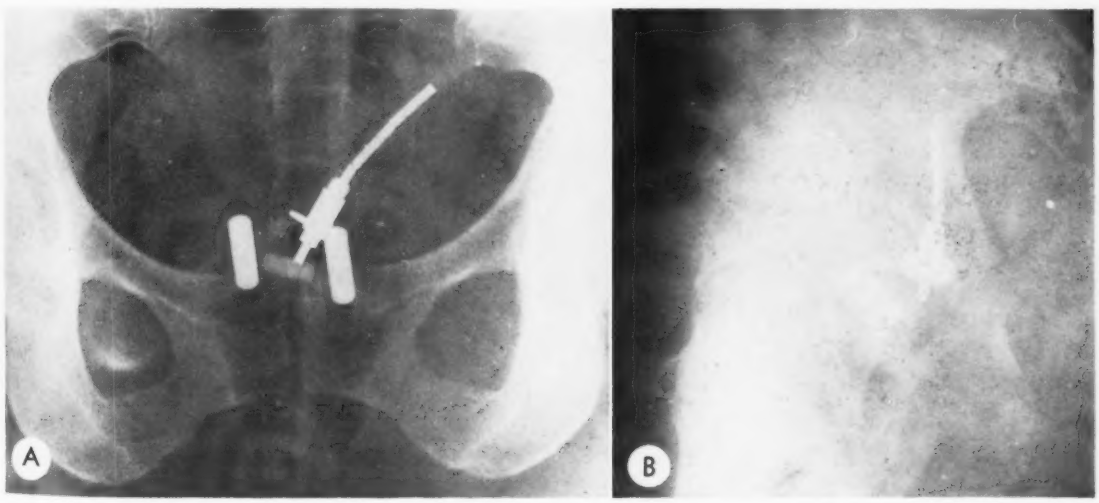


Fig. 6. (*A* and *B*) Case vii.

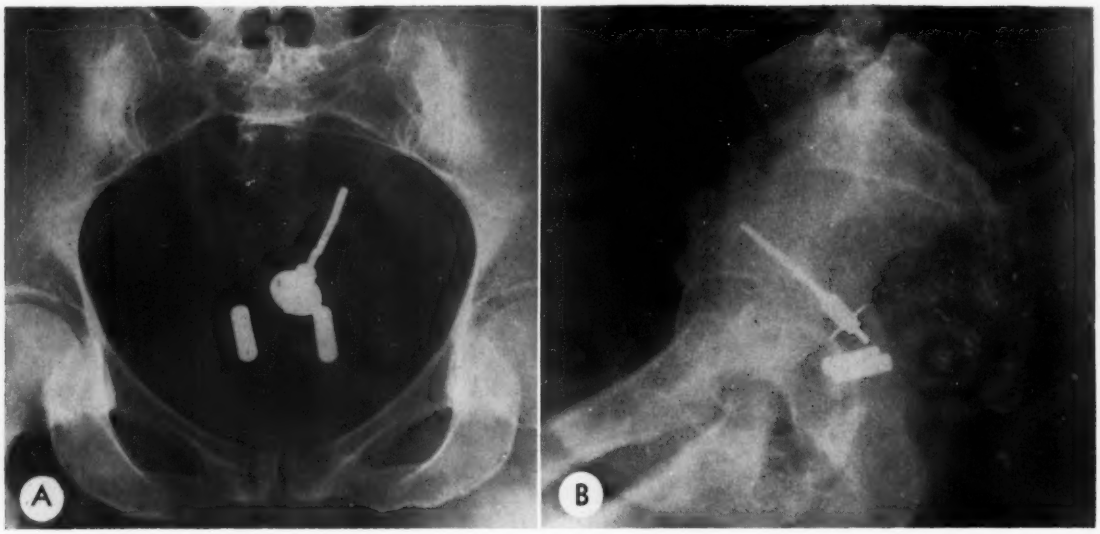


Fig. 7. (*A* and *B*) Case viii.

created. Granted that such a designation in the face of what is considered adequate therapy under otherwise normal conditions is extremely tempting, it, nevertheless, behooves us to carefully re-evaluate our acceptance of it so readily.

In simple terms, absolute radioresistance does not exist. Any tissue, normal or malignant, can be destroyed if enough radiation is applied. Radioresistance in therapy is really the relative resistance of normal versus cancerous tissue. This relative sensitivity of various tissues is the very essence on which radiation therapy is based. It must be recognized that the term radioresistance as it is designated here refers only to the relative sensitivity of tissues within the limits of toleration of normal tissues and therefore within the practical limits of applied radiation therapy.

## MATERIAL AND METHOD

Attempts to correlate the "radioresistance" of a cervical tumor, prior to its

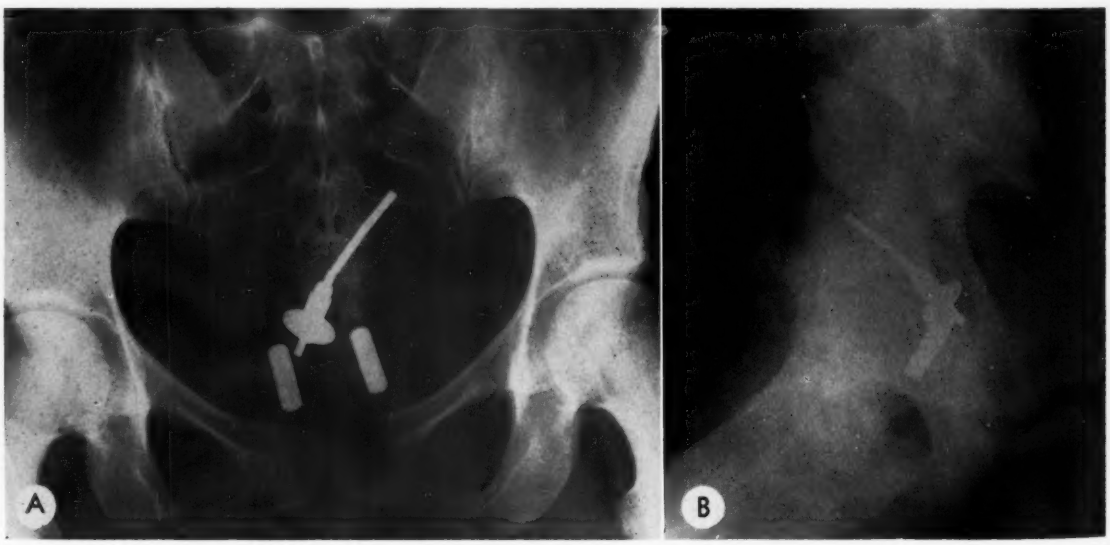


Fig. 8. (*A* and *B*) Case ix.

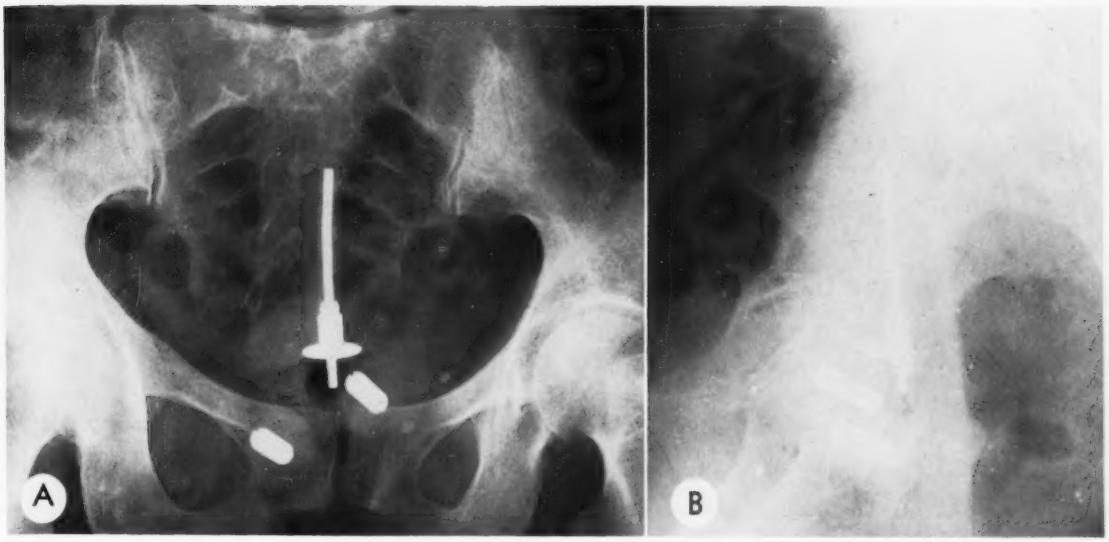


Fig. 9. (*A* and *B*) Case xii.

treatment by irradiation, with the actual end results have not been successful in our hands. The three methods utilized in this endeavor included: first, a correlation of the histologic-grading using Broders'[2] classification with the tumor response; secondly, attempted correlations of vaginal smears and tumor response prior to treatment as described by Graham and Graham;[5,6] and thirdly, the method described by Glücksmann and Way[3,4] of studying the modification of cell types after small amounts of irradiation. No valid correlations were obtained with these three methods. A review of the literature shows that there is a similar lack of confirmation by others of the value of such tests.

The insignificance of radioresistance as a

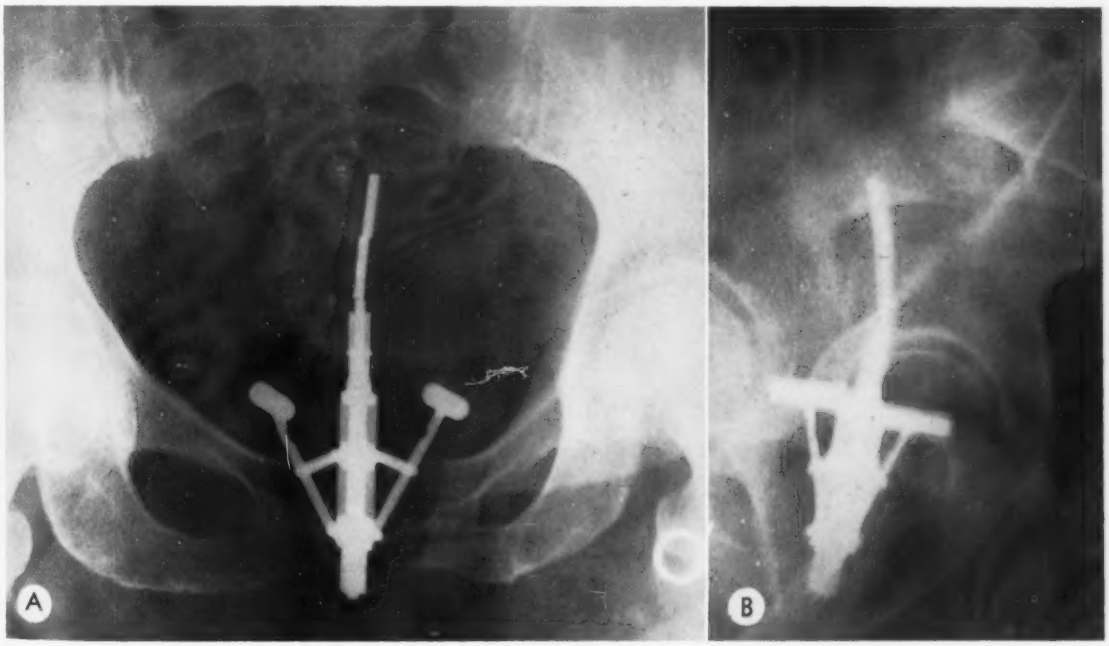


Fig. 10. (*A* and *B*) Case xiii.

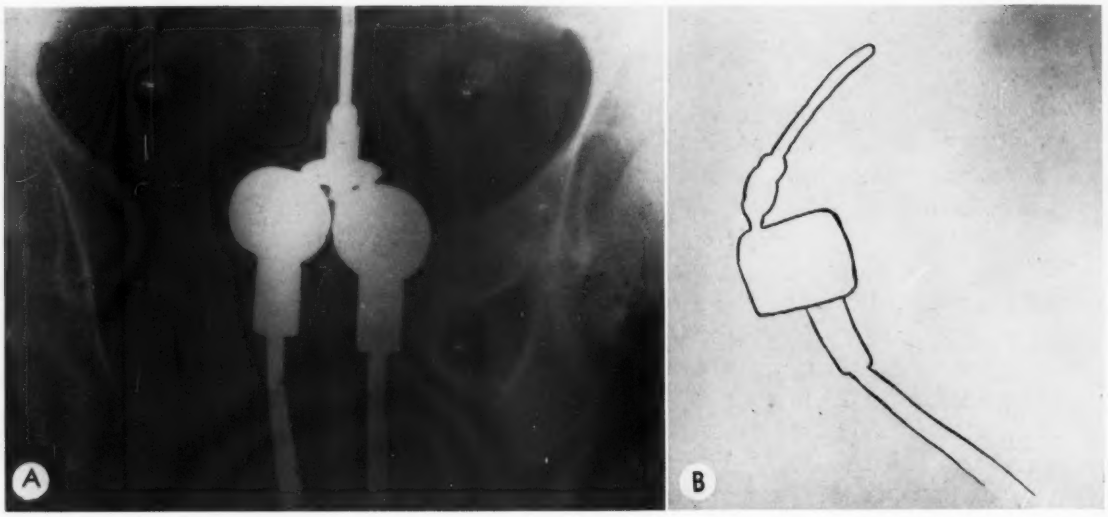


Fig. 11. (*A* and *B*) Case xiv.

cause for failure of radiation therapy became evident when we began to carefully re-evaluate the failure cases treated since 1950. During the years 1950 to 1956, a total of 422 cases of primary carcinoma of the cervix, Stages I, II and III were treated at the Washington University Clinics. Table I is a compilation of the results.

A review of the 124 failure cases revealed that a total of 14 patients died of distant metastases without pelvic involvement. By far, the majority of failures occurred in the group with persistent disease in the pelvis. Of these only 23 had persistent disease locally at the cervix and vagina; the other 87 cases were failures of treatment due to

Table I

Carcinoma of the Cervix 1950–1956
Stage I, II and III

| | |
|---|---|
| Alive and well | 268 |
| Dead of intercurrent disease | 13 |
| Lost to follow-up | 17 |
| Distant metastases without pelvic involvement | 14 |
| Persistence of carcinoma at cervix or vagina | 23 |
| Persistence of carcinoma in pelvis without involving cervix or vagina | 87 |
| Total | 422 |

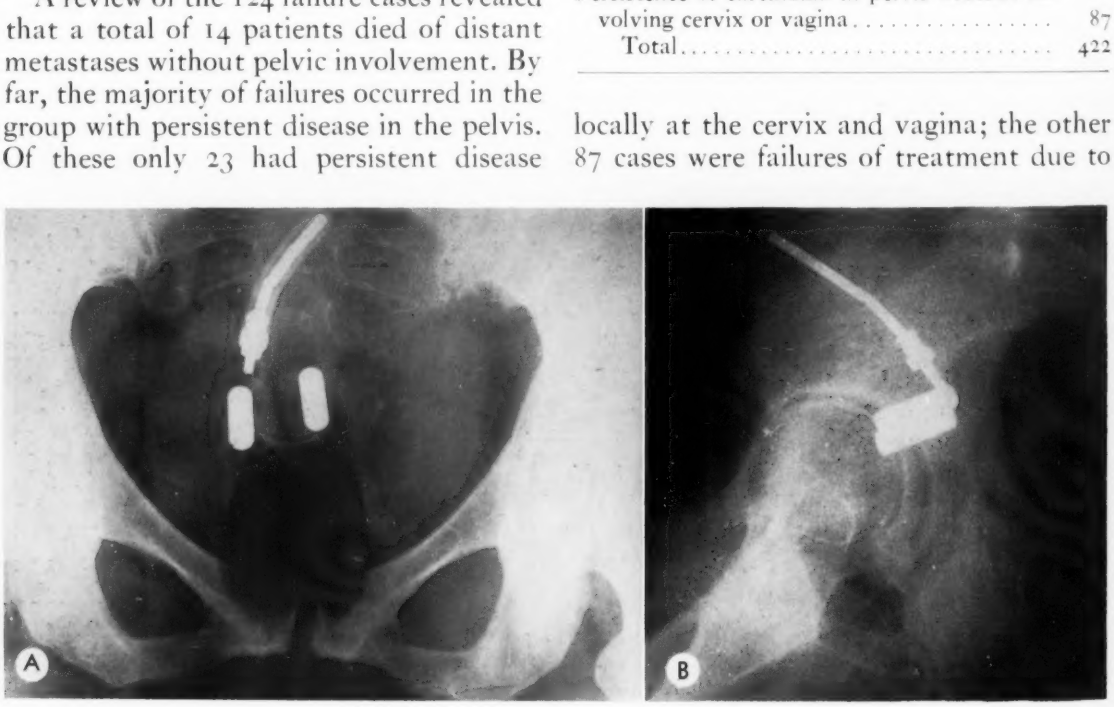


Fig. 12. (*A* and *B*) Case xv.

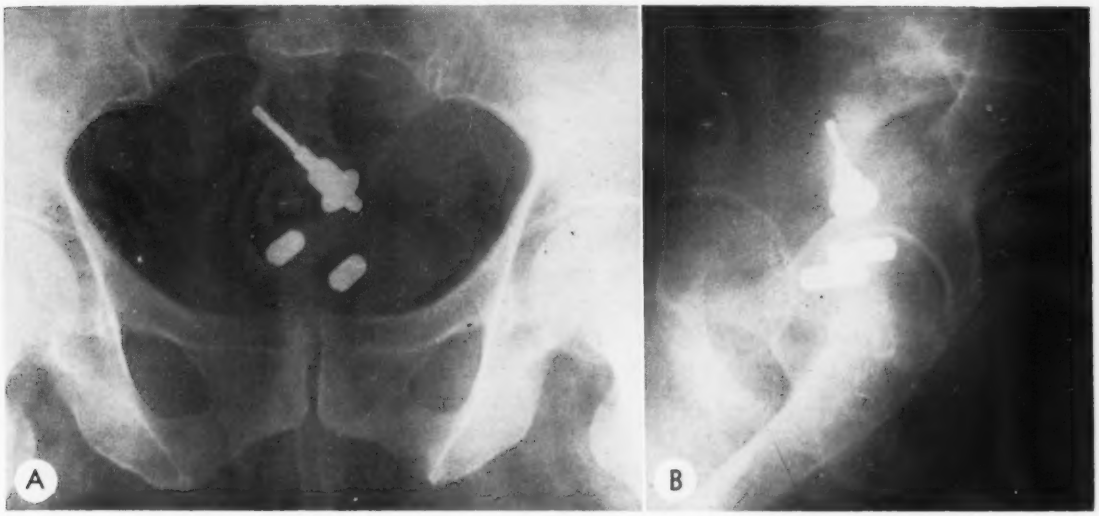


Fig. 13. (*A* and *B*) Case xvi.

persistence of disease in the lateral pelvis with or without associated distant metastases.

It would be unreasonable to consider all these failure cases as due to radioresistance. Certainly, the group of patients who died of distant metastases without local recurrence cannot be included. In the same way it is believed unlikely that failures in the group of patients who died with disease in the lateral pelvis not involving the cervix and its immediate confines were due to radioresistance. The anatomic and physical factors involved might have been such as to make it impossible to deliver a dose of radiation to the lymph node areas comparable to that received at the cervix. It would be more reasonable to assume that these failures were due to underdosage, particularly when the radiation was successful in eradicating the local lesion.

It would not be out of line, however, to assume that failure to achieve eradication locally at the cervix was due to radioresistance. Therefore, the 23 cases listed as having persistent cancer of the cervix, or

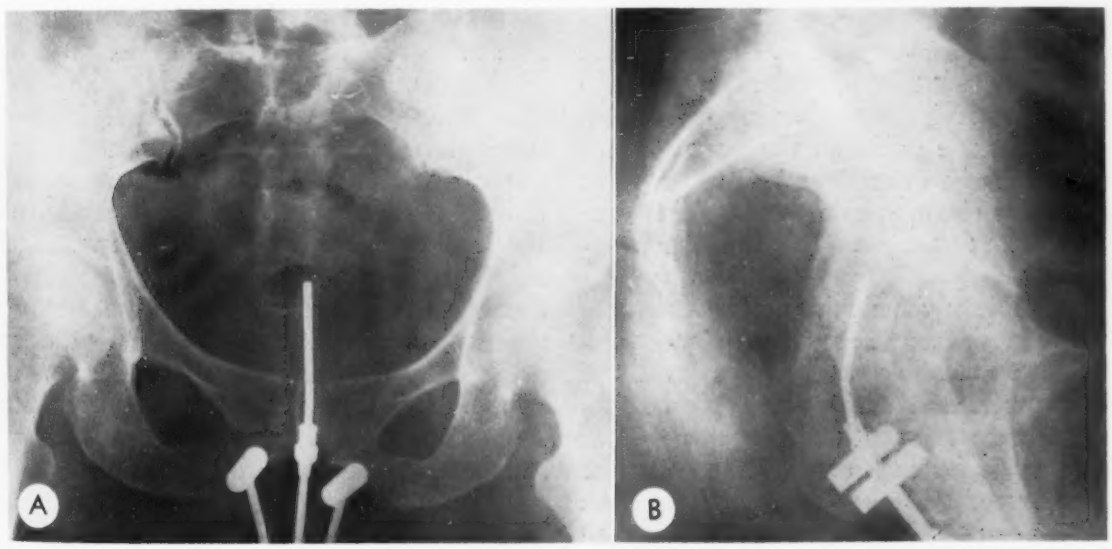


Fig. 14. (*A* and *B*) Case xviii.

within 2 cm. of the midline or the upper vagina, with or without disease elsewhere, could be termed radioresistant. Nevertheless, we must consider one other possibility. The application of radium is sometimes difficult because of the anatomic features of the cervix, vagina and the tumor. An assumption that the procedure has been accomplished satisfactorily because it so appears at the time of packing is not necessarily so. A critical appraisal of radium application procedures performed during the last ten years convinced us of the great care and effort necessary to obtain completely satisfactory insertions. Before considering all of these 23 cases as failures due to radioresistance, it was necessary to determine whether the intended dose was delivered. To do so, the 23 failure cases were re-evaluated. Roentgenograms were available for study in only 18 of these cases. The doses delivered to various points in the pelvis and particularly the areas of recurrence at the cervix, fornices, or immediate parametria were recalculated as best as possible from the roentgenograms of the radium applications and associated factors. The site of recurrence was estimated as best as possible on the roentgenogram. Measurements from the end or center of each of the radium tubes to the site of recurrence were carried out. Corrections for magnification of the roentgenograms were made. Dose tables[9] were used to define the dose that each tube of radium delivered to this point and the totals were calculated. A comparable point on the opposite side was similarly defined and the dosage at this point also was calculated on the same basis. The findings are of particular interest.

In Table II the significant data relating to each failure case are listed. Roentgenograms of the 18 cases which were available are reproduced showing one typical application from two or three that might have been made for each case (Fig. 1–18). The majority of these applications were done with separate intrauterine tandems and vaginal ovoids. In general, the Manchester system[7] of distribution was attempted. The tandems usually contained sources of 20–10–5 mg. of radium in that order from the top, and the ovoids contained 20–20 mg. sources. At first glance it may seem impossible to obtain discrepancies of the order shown in the table. However, if one recalls the isodose curves surrounding radium sources and considers the proximity of these sources to the cervix and the upper vagina, distances as short as 1 cm. may cause tremendous differences in the doses received by the tissues. This is particularly so when the error is compounded by derangement in both the tandem and the ovoids. Obviously, in retrospect none of these applications were satisfactory. Since in most of the cases a separate tandem and ovoids were used, it was often difficult to align the sources accurately in relationship both to each other and to the cervix and tumor. Ideally, their distribution should produce a uniform isodose pattern in the pelvis. This does not imply that fixed tandem-ovoid applicators are faultless. Though the relationship of tandem and ovoids to each other is maintained, other mistakes do occur.

In several of the failure cases, it became obvious that the radium colpostat was allowed to remain in too low a position or too far from either the cervix or the fornices, most often because of failure to recognize or locate the cervix or upper vagina on the roentgenogram. Even though a uniform isodose pattern was produced, it still resulted in unrecognized low dosages at the tumor site. Similarly, the lowermost tandem source was at times too high above the level of the ovoids when widely separated. In these instances the resultant isodose pattern did not contain the tumor within its cancerocidal levels. With our present day experience, none of these would be tolerated and either would be corrected satisfactorily or other means to deliver adequate radiation would be sought.

In the hope of avoiding any such future errors, the present procedure for radium application is carefully planned. All pa-

TABLE II

RADIATION TREATMENT FAILURES

| Case | Patient | Age | Stage | Year Treated | Recurrence (mo.) | Radium Treatments | | | Supplemental Treatments | | Dose at Area of Recurrence (r) | Dose at Comparable Area on Opposite Side (r) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | no. of applications | no. days apart | total mg. hr. | roentgen therapy r | roentgen therapy no. of ports | | |
| I | E.P. | 34 | I | 1950 | 18 | 2 | 14 | 7,225 | 2,400 | 4 | 3,960 | 20,768 |
| II | V.S. | 59 | I | 1950 | 34 | 2 | 12 | 5,500 | 1,600 | 6 | 4,050 | 16,350 |
| III | M.P. | 56 | II | 1950 | 30 | 2 | 14 | 6,850 | 2,400 | 6 | 4,500 | 22,660 |
| IV | M.F. | 35 | II | 1950 | 11 | 2 | 26 | 5,440 | 1,600 | 4 | No roentgenograms available | |
| V | C.S. | 42 | III | 1951 | 10 | 2 | 28 | 6,400 | 2,700 | 6 | 4,150 | 17,470 |
| VI | S.D. | 46 | II (stump) | 1951 | 46 | 2 | 14 | 5,900 | 2,400 | 6 | 4,800 | 21,100 |
| VII | L.B. | 49 | II | 1951 | 11 | 2 | 21 | 7,410 | 2,400 | 4 | 5,455 | 10,675 |
| VIII | F.C. | 48 | III | 1951 | 10 | 2 | 14 | 6,590 | 2,800 | 4 | 4,765 | 17,025 |
| IX | L.H. | 36 | II | 1951 | 12 | 2 | 8 | 5,330 | 2,400 | 6 | 5,340 | 14,230 |
| X | L.W. | 43 | II | 1951 | 9 | 2 | 17 | 5,575 | 2,400 | 4 | No roentgenograms available | |
| XI | L.B. | 29 | II | 1952 | 7 | 2 | 21 | 6,640 | 2,400 | 4 | No roentgenograms available | |
| XII | G.J. | 67 | I | 1952 | 12 | 2 | 8 | 7,200 | 2,400 | 4 | 4,840 | 5,400 |
| XIII | F.W. | 63 | II | 1952 | 20 | 2 | 28 | 9,000 | 2,200 | 6 | 7,064 | 7,740 |
| XIV | M.D. | 67 | III | 1953 | 14 | 2 | 20 | 5,150 | 3,200<br>2,000 | 2<br>4 | 5,070 | 20,320 |
| XV | C.N. | 53 | III | 1953 | 11 | 2 | 14 | 7,100 | 2,400 | 4 | 4,980 | 18,030 |
| XVI | L.C. | 34 | III | 1953 | 12 | 3 | 40 | 8,100 | 3,200 | 6 | 6,360 | 14,412 |
| XVII | R.S. | 35 | III | 1953 | 4 | 2 | 14 | 6,820 | 2,400 | 4 | No roentgenograms available | |
| XVIII | D.M. | 55 | II | 1954 | 14 | 2 | 27 | 7,950 | 140 mc $Au^{198}$ | | 7,418 | 7,278 |
| XIX | A.R. | 49 | I | 1954 | 11 | 2 | 21 | 7,625 | 140 mc $Au^{198}$ | | 7,140 | 7,480 |
| XX | G.S. | 69 | III | 1955 | 22 | 2 | 14 | 8,700 | 130 mc $Au^{198}$ | | 6,000 | 16,790 |
| XXI | J.P. | 47 | I | 1955 | 8 | 2 | 10 | 7,430 | 130 mc $Au^{198}$ | | No roentgenograms available | |
| XXII | H.A. | 39 | III | 1956 | 17 | 3 | 34 | 9,800 | 140 mc $Au^{198}$ | | 6,120 | 6,400 |
| XXIII | L.K. | 59 | III | 1956 | 24 | 2 | 27 | 8,600 | 120 mc $Au^{198}$ | | 6,480 | 6,480 |

tients are anesthetized and under completely sterile precautions the radium is inserted. The cervix is tagged by one or two silver vascular clips, which are clamped on a catgut suture and fixed in place. We have found this to be more satisfactory than direct clipping, since clips are apt to fall off, start bleeding or traumatize the tumor. After the radium is inserted, direct measurements with a scintillation counter[1] are made at the cervix and vaginal fornices. After packing the colpostat in place, measurements are also taken in the bladder and rectum, both midline and laterally. These measurements are extremely helpful in defining the adequacy of the application and the subsequent time exposures for the radium sources. Following this, anteroposterior and lateral roentgenograms are taken before the patient leaves the operating room and while still under anesthesia. The darkroom adjoins the operating room and within a few minutes roentgenograms are ready for review. If these are satisfactory, the patient is taken to the recovery room; if not, the necessary adjustments are

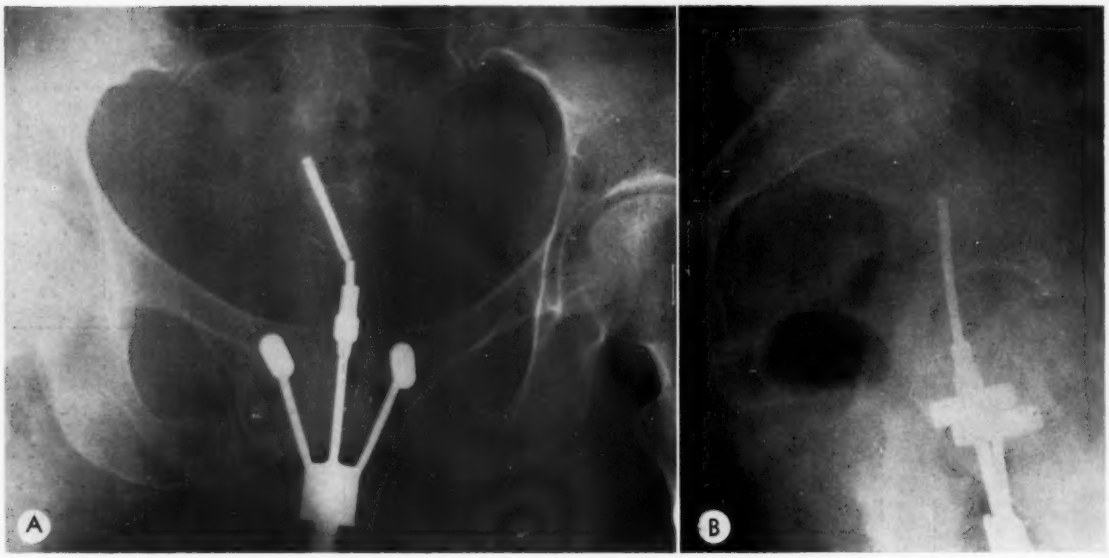


Fig. 15. (*A* and *B*) Case xix.

made, even to the point of changing the entire colpostat, if necessary; repeat roentgenograms are taken until a satisfactory insertion is obtained. When the rentgenograms are dry, they are again reviewed and calculations of the dose at points A, B and cervix are made. The total exposure time is then determined.

In view of the findings, as shown in Table II, we cannot consider these 18 cases as failures due to radioresistance. If a dose evel of 8,000 r is accepted arbitrarily as a minimal cancer dose, the cause of failure in all 18 cases is evident. This dose cannot be considered excessive. It can be delivered with relative ease to the entire cervix and upper vagina by intracavitary radium. It is not intended to belabor and stress the point of numerical dosages. The many factors which enter into radiation success have been discussed already. Assuredly, there are several cases in the successful group in which the measurements and insertions were in the same range as those

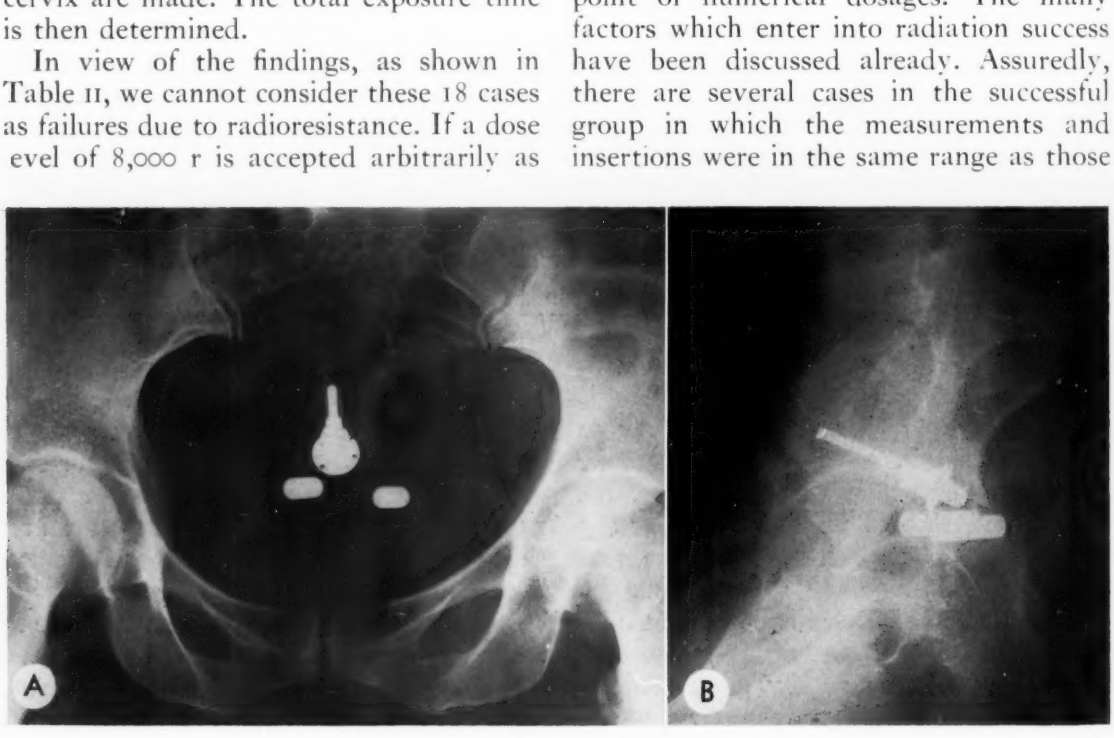


Fig. 16. (*A* and *B*) Case xx.

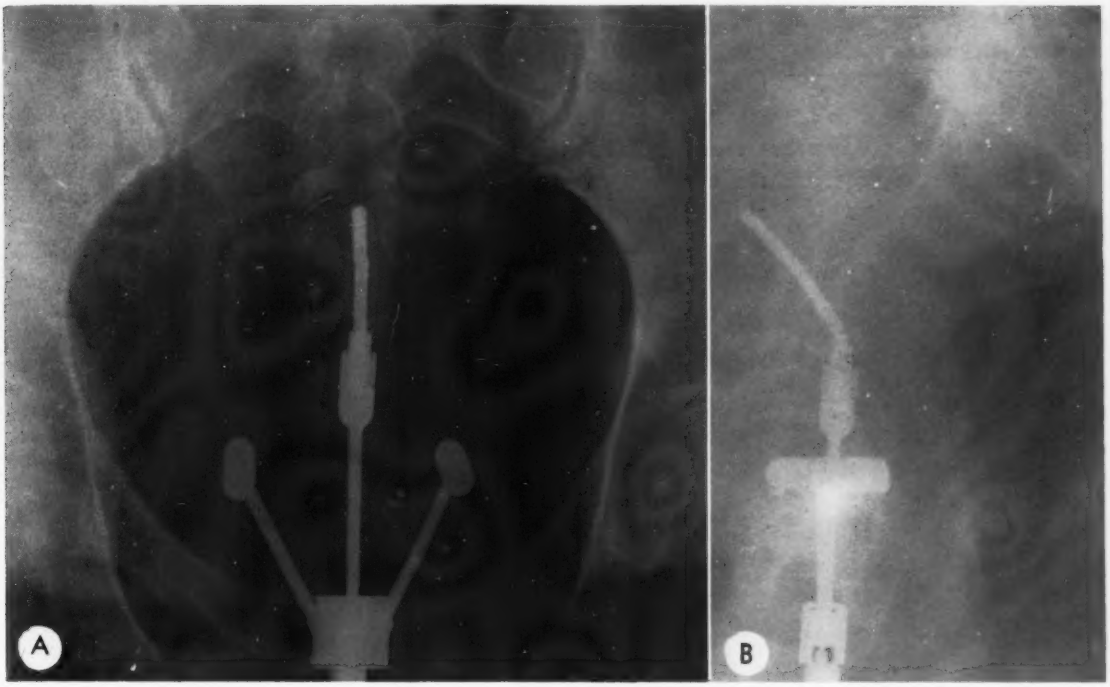


Fig. 17. (*A* and *B*) Case xxii.

in the failure cases. The difference probably lies in the fact that these were either extremely sensitive tumors or cases in which no tumor existed at these particularly low dosage points. It may be said that some factors were in operation which made possible the eradication of the tumor at these dose levels.

There is, of course, no certainty that higher dosages would have altered the subsequent course of the failure cases. It must be emphasized, though, that radiation failures did not occur when the dosage range was well within the practical limits of therapeutic techniques.

On the basis of our work, we feel that it

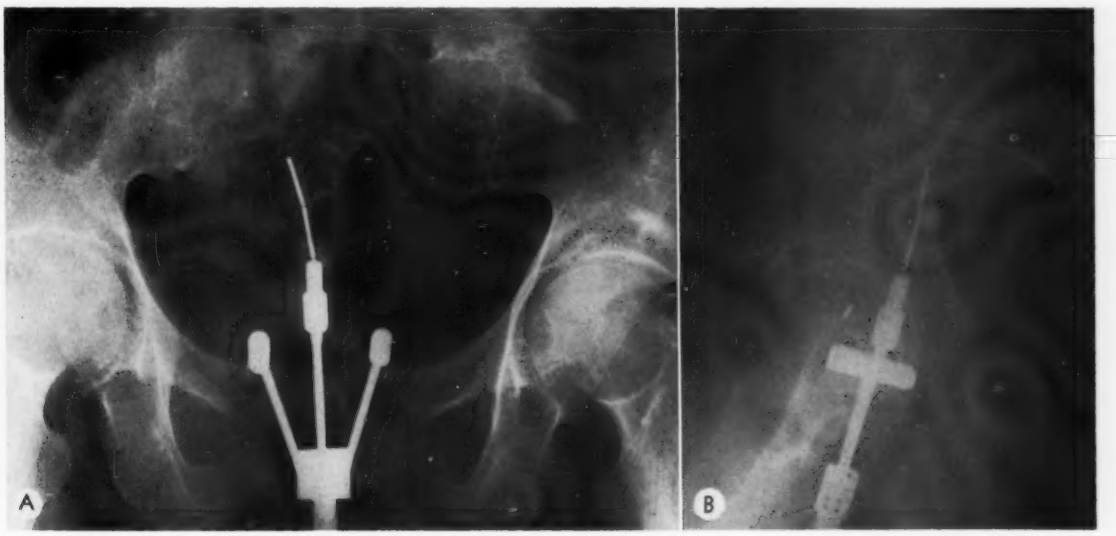


Fig. 18. (*A* and *B*) Case xxiii.

is necessary to modify our views regarding the subject of radioresistance. Before a tumor is regarded as radioresistant, inadequate therapy as the cause must be ruled out. More important, every possible means must be taken to avoid such errors in the future. The routine of a radium application must include all possible checks and to be accepted as satisfactory must meet the strictest criteria.

## CONCLUSION

As a result of our experience we cannot accept the incidence of radioresistance in cancer of the cervix to be more than 1.2 per cent (5 of 422 cases). In all probability the incidence would be less if we were to appraise these additional 5 cases. The study shows the relative infrequency of radioresitance as the causative factor in radiation therapy failures. Such a low incidence does not deserve the attention that presently is being paid to it. Neither does it justify radical alterations in therapy, but rather helps emphasize the value of irradiation in the treatment of this disease. The ready acceptance of radiation failures as being due to radioresistance is a pitfall to be avoided. We believe that many cases are radiation failures not because of radioresistance but because of improper therapeutic techniques of the type indicated in our 18 cases.

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# URETERAL OBSTRUCTION IN STAGE III CANCER OF THE CERVIX RELIEVED BY LOW INTENSITY RADIUM NEEDLE IMPLANTATION*

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THE importance of ureteral obstruction produced by parametrial invasion in cancer of the cervix with secondary uremia and infection was described by Chavannay[4] in 1899 and numerous similar articles appeared in the 1920's. Since both roentgen-ray and radium therapy were being used at that time, many were prone to attribute the ureteral occlusions discovered at autopsy to the fibrosis produced by these new methods of treatment.

## HISTORICAL REVIEW

That such could indeed be the case was brought forcibly to our attention when a postmortem examination of one of our early patients revealed bilateral ureteral obstruction from radiation fibrosis with no demonstrable evidence of residual cancer of the cervix. Schmitz[18] reported a similar experience in 1920 and soon afterwards we started some studies aimed at the elimination of such serious sequelae. Dr. Fred Rogers, Professor of Physiology in the old Baylor Medical School in Dallas, offered to help with some experiments designed to determine the radiosensitivity of the ureter of the dog. His unusual skill as a dog surgeon enabled us to carry out this work with very few mishaps.

At that time we were attempting to control parametrial invasion with the implantation of monel steel needles, each of which contained 6.25 mg. of radium in an active length of 7.5 mm. and had a wall thickness of 0.35 mm., which permitted the emission of both beta and gamma rays. They were usually left in place for 8 to 10 hours. Of course, in the light of our present knowledge we know that the loading was too high, the filtration inadequate and the time too short but our technique was similar to that generally used in this country in the 1920's.

In the dog experiments, the left abdomen was opened and two of the steel needles were placed about 1 cm. apart on either side of the mid-left ureter for periods varying from 4 to 8 hours. Autopsies done 2 to 3 weeks later revealed complete ureteral obstruction and hydronephrosis produced by doses as low as 75 mg. hr. We were not capable of estimating these doses in roentgens when this work was done but recent calculations carried out with the help of Edith Quimby indicate that the combined beta and gamma radiation delivered to the ureter was somewhat in excess of 5,000 r. The details of this investigation were published in 1926.[7]

Some previous experiments, in which a 50 mg. well-filtered radium capsule was placed in contact with the ureter for 5 hours without producing serious damage, led us to believe that beta rays caused the ureteral strictures when the steel needles were used. With these data available, all steel needle implantations were discontinued and attempts were made to control ureteral obstructions secondary to parametrial invasion by various radium capsule and roentgen-ray techniques combined with ureteral dilatations, indwelling catheters, ureteral transplants, nephrostomies and ureterostomies. The results of this work, which produced marked palliation but no cures of long duration, were published in 1928.[9,10]

The use of radioactive sources in the parametria has always been intriguing because such a technique should enable the

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radiotherapist to limit a large dose to the affected region, thereby protecting such radiosensitive normal structures as the bladder and the bowel. In the early 1920's Burnam[2] and Levin[6] recommended the insertion of glass radon seeds through the vagina or peritoneum as a useful procedure. However, Levin noted a severe reaction in the tissues surrounding these implants and observed that many of the patients developed a high fever soon after they were inserted. Our experiments have led us to believe that even the seeds developed later, which provided a filtration of 0.3 mm. of gold or platinum, could not be used safely because they emitted some beta radiation.

More recently, radioactive isotopes have been employed for interstitial therapy. Allen, Sherman, and Arneson[1] report regression of malignant invasion of the parametria following the local injection of radioactive colloidal gold. Since beta rays constitute about 90 per cent of the radiation emitted by this substance, it seems logical to assume that ureteral, bladder and bowel damage should appear when injections are made near these structures. Carlin,[3] who has studied 22 patients with urologic symptoms from a series of 135 patients treated by Allen, Sherman and Arneson, believes that ureteral strictures and bladder injuries observed in at least 10 cases with no residual cancer could be attributed to the effect of the colloidal gold. He also believes that some of the patients with urologic damage were not included in his series because they went elsewhere for treatment or had so few symptoms from the ureteral obstructions that they were not referred for urologic investigation. The incrimination of a single method was found to be very difficult because all of the patients except 1 also received surgery, radium or roentgen therapy or a combination of these methods. Since beta rays penetrate only a few millimeters of tissue, the evidence presented suggests that stricture can be expected only when the colloidal gold is injected in close proximity to a ureter. The low incidence of such sequelae reported may result from the difficulty experienced in obtaining an even distribution of the injected material, particularly when the parametrium is infiltrated with carcinoma.

Obviously, the best form of interstitial radiation should be capable of destroying cancer cells while producing the smallest number of serious sequelae. In 1924 Regaud[16] postulated that such criteria could best be met by using very low intensity sources, heavy filtration allowing the emission of only gamma rays and relatively long treatment times. The so-called low intensity radium needles, which were first made available to us in 1930, have been found useful in carrying out such a plan of therapy.[11] They were used cautiously in the cervix and then in the vaginal walls and parametria. The good results reported by Pitts and Waterman[15] in 1940 encouraged us to use them more extensively and descriptions of our techniques were published in 1948[12] and more recently in 1957.[13]

Our conviction that low intensity radium needles could be implanted so as to produce no ureteral damage was substantiated by some experimental work published by Clayton[5] in 1951. He placed a platinum needle loaded with 2.4 mg. of radium in 4.0 cm. of active length on either side of the ureter in dogs for 168 hours and found no changes at the time of autopsy. The needle wall thickness was 0.5 mm.

## TREATMENT

In a patient with a large cervical carcinoma complicated by a ureteral stricture produced by malignant invasion of the parametrium, treatment consists of a cylindrical implant of long needles in the periphery of the primary tumor often augmented by a long 25 mg. well-filtered capsule in the cervical canal and one or two vertical rows of similar needles in the involved parametrium. The radium remains in place for 7 days, except when the primary tumor is relatively small, in which event the central capsule is removed in 3 to 4 days or not used at all. Calculations made for some

such radium patterns indicate that point doses varying from 10,000 to 15,000 gamma r can be delivered to the parametrium in this manner and adequate doses can be given near the pelvic wall. Aside from a low grade temporary proctitis, very few sequelae have occurred and most of the patients have developed no persistent symptoms.

It is our belief that squamous cell carcinoma growing in metastatic nodes can be completely controlled only with doses of radiation larger than those used to eradicate the primary lesion. Experience has indicated that such nodes growing in the neck can be cured for long periods of time without irreparable normal tissue damage when such large doses are delivered with a combination of implanted low intensity radium needles and conventional roentgen therapy given while the needles are in place. In the neck, air doses of 350 r are given to a 10×10 cm. port daily until a total of 2,100 r has been reached, using conventional roentgen-ray equipment fully described elsewhere.[14] In the pelvis, air doses of 200 r have been given daily with an 80 cm. target skin distance to opposing 15×15 cm. anterior and posterior ports until 1,200 r has been delivered to each port while the parametrial needles are in place. The tissue dose of roentgen rays delivered to the midplane of the average pelvis in this manner amounts to approximately 1,400 r. In the more advanced cases this treatment has been repeated 6 weeks after the removal of the needles without producing any evidence of visceral damage.

## REPORT OF CASES

The following case histories show that malignant parametrial invasion can be controlled and that in some cases ureteral obstructions can be relieved and renal function restored following the implantation of low intensity radium needles.

Case I (Fig. 1, *A* and *B*). This thirty-eight year old woman was admitted to the hospital complaining of a bloody discharge and severe pain referred from the right flank to the thigh for 3 months.

The blood sugar was 192 mg. per cent and she had an anemia. The cervix was hard, measured 4.0 cm. in diameter and was displaced to the right by parametrial infiltration which extended entirely to the pelvic wall. The biopsy report was squamous cell carcinoma, Grade III. An intravenous pyelogram revealed no obstruction of double ureters on the left side and no visualization on the right side.

The diabetes was controlled by medical treatment after which ten 2.4 mg. radium needles were placed in a cylindrical pattern in the periphery of the cervical tumor, one 2.4 mg. needle in the center of the mass and six 3.0 mg. needles in two vertical rows well out in the right parametrium for 7 days. While the radium was in place, 200 r (air dose) was given daily to each of two 15×15 cm. ports laid out over the anterior and posterior right pelvis for 6 consecutive days using 260 kv. equipment, a filter of ½ mm. of copper and 1 mm. of aluminum and a target skin distance of 70 cm. The patient was large and had a pelvic thickness of approximately 22 cm.

At six weeks the pain was almost completely relieved and she felt much better. The induration in the right parametrium was much less, the upper vagina was somewhat contracted and all visible evidence of carcinoma was gone leaving a gray radium reaction on the face of the cervix.

Intravenous urography done at 6 months visualized normal kidney pelves on both sides. However, the pleura on the right side was infiltrated with carcinoma and the patient died of generalized metastases at 1½ years with no demonstrable evidence of cancer in the pelvis.

Case II (Fig. 2, *A* and *B*). This sixty-eight year old woman was admitted to the hospital complaining of weight loss, weakness, low back pain and vaginal hemorrhage for 2 months. An intravenous urogram showed poor concentration of the opaque medium and bilateral hydronephrosis at 25 minutes. Pelvic examination revealed the cervix to be replaced by a friable bleeding tumor measuring 6 cm. in diameter and fixed in the pelvis by infiltration in both parametria extending to the pelvic walls. The biopsy report was adenocarcinoma.

Palliative therapy was undertaken by removing the presenting portion of the tumor by electrocoagulation and inserting eight 1.33 mg.

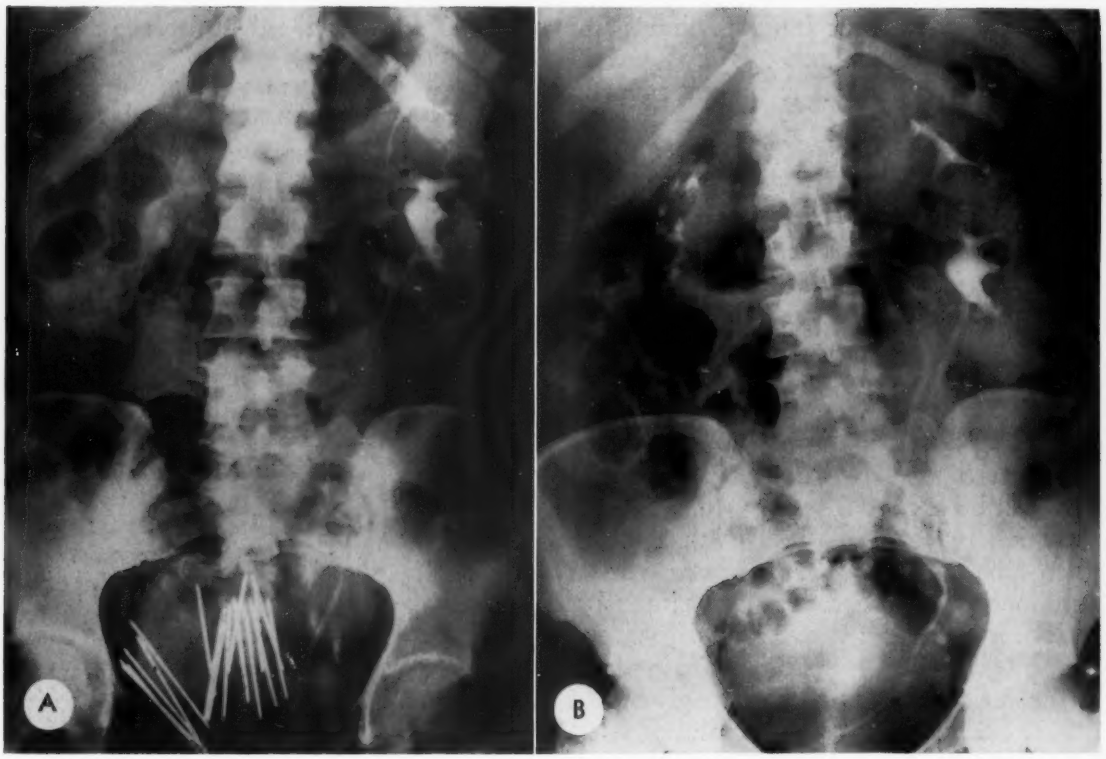


Fig. 1. Case I. (*A*) Nonvisualization of the right kidney pelvis and ureter due to ureteral obstruction secondary to malignant invasion of the right parametrium extending entirely to the pelvic wall. (*B*) Visualization of the normal right kidney pelvis 6 months after the implantation of low intensity radium needles in the cervix and right parametrium and the addition of a small amount of conventional roentgen therapy.

radium needles in the center and fourteen 2.4 mg. needles in the extreme periphery of the mass for 7 days.

At 4 months the symptoms were relieved and she had gained 15 pounds. The cervical mass was almost completely gone but induration could still be felt in the parametria. At 6 months the cervix was smoothly healed but she complained of some pain in the left groin. An intravenous urogram showed a normal kidney pelvis on the right side but the left pelvis was not visualized. However, a retrograde pyelogram made after inserting a catheter through a partial stricture in the lower left ureter revealed a moderate hydronephrosis on the left side. A course of roentgen therapy was given to the sides of the pelvis but the patient was then lost to follow-up.

Case III (Fig. 3, *A* and *B*). This seventy-six year old woman was admitted to the hospital complaining of vaginal bleeding and pain in the lower back and hips for several months. Roentgenographic examinations revealed a solitary stone in the gallbladder, infiltration at the bases of both lungs and a hydronephrosis on the right side, demonstrated by a retrograde pyelogram. The cervix was very hard and large and was fixed by bilateral parametrial invasion. A metastatic tumor measuring 2.5 cm. in diameter was seen in the lower anterior vaginal wall just behind the ureteral orifice. A cervix biopsy was reported as squamous cell carcinoma, Grade II.

A well-filtered 50 mg. radium capsule was placed in the cervical canal for 24 hours and ten 2.4 mg. radium needles were inserted in a cylindrical pattern well out in the periphery of the tumor of the cervix with four 1.33 mg. needles implanted longitudinally in the vaginal metastasis for 7 days.

At 4 months she felt much better and was free of all pelvic symptoms. At 6 months she still felt well except for weakness. A pyelogram indicated that the right kidney pelvis was normal. The vaginal tumor had healed and the upper vaginal walls were sealed over a small cervix. However, the liver was markedly en-

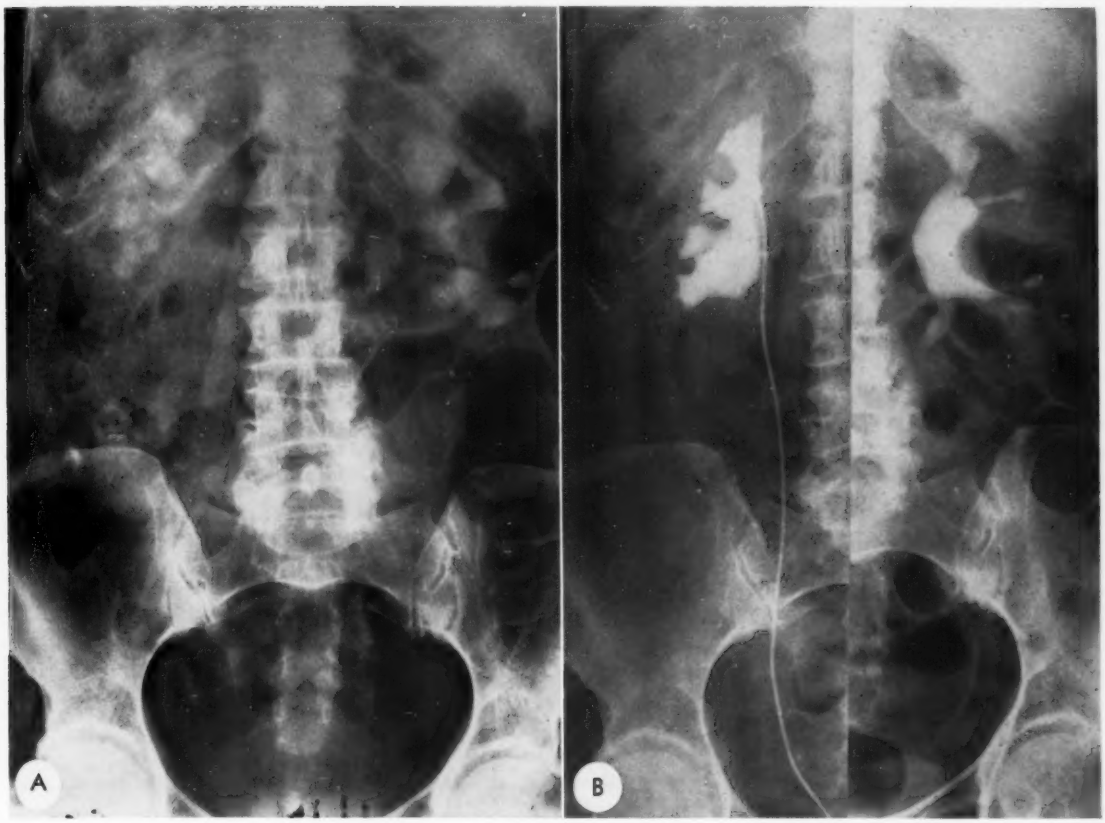


Fig. 2. Case II. (*A*) Obstruction of both ureters with poor visualization of moderately dilated kidney pelves secondary to malignant invasion of both parametria. (*B*) The condition is definitely improved at 6 months after low intensity radium needle implantation in a large cancer of the cervix and proximal parametria.

larged and the patient died of generalized metastases at 7 months.

Case IV (Fig. 4, *A*, *B* and *C*). This thirty-eight year old woman was admitted to the hospital complaining of right sided pelvic pain and postcoital bleeding of two months' duration. An intravenous urogram made by her urologist before admission revealed an obstruction low in the right ureter and a moderate degree of hydronephrosis. There was a double ureter and double kidney on the left side without evidence of hydronephrosis. The cervix was replaced by friable tumor tissue which extended to the right pelvic wall producing partial fixation of the cervix. The biopsy report was invasive squamous cell carcinoma.

Bleeding was controlled with electrocoagulation. Eleven 2.4 mg. radium needles were inserted in the periphery of the cervical tumor and four 3.0 mg. and one 2.4 mg. needles were inserted in a vertical layer well out in the right parametrium for 7 days. A dose of 200 r (air dose) was given daily to 15×15 cm. ports laid out over the anterior and posterior right pelvis on 3 consecutive days, following the radium needle implantation. The factors were 260 kv., a 70 cm. target skin distance and a filter of 0.5 mm. of copper and 1.0 mm. of aluminum.

On the fourth day roentgen therapy was stopped because the patient developed a pyelonephritis but the radium was left in place and antibiotic therapy was started. However, at 6 weeks she developed another attack of pyelonephritis and pyelograms done at home showed no improvement in the right sided hydronephrosis. A nephrectomy was considered but not carried out.

At 4 months she felt much better. The double ureters on the left side showed some dilatation but the pelves of both kidneys had a normal size.

At 1½ years she had gained about 38 pounds,

FIG. 3. Case III. (*A*) Obstruction of the right ureter with hydronephrosis secondary to malignant parametrial invasion is completely relieved (*B*) 6 months after the implantation of low intensity radium needles into a carcinoma of the cervix and the right parametrium.

FIG. 4. Case IV. (*A*, *B* and *C*) Hydronephrosis and dilatation of the right ureter secondary to malignant invasion of the right parametrium was relieved in 4 months by the implantation of low intensity radium needles in a cancer of the cervix and the right parametrium for 7 days, with the addition of a small amount of conventional roentgen therapy.

had no pelvic symptoms and felt well. The kidney pelves still had a normal size and pelvic examination revealed no evidence of cancer.

Case v (Fig. 5, *A–D*). This forty-seven year old woman was admitted to the hospital complaining of repeated vaginal hemorrhages and severe pain in the right pelvis referred to the thigh of 12 months' duration. She received 4 blood transfusions before she was admitted and another one on the day of admission.

She was bleeding freely from a friable cervical mass which had invaded the adjoining vaginal walls and infiltrated the parametrium entirely to the right pelvic wall. The biopsy report was squamous cell carcinoma, Grade II to III.

The hemorrhage was controlled with electrocoagulation. Twelve 2.4 mg. radium needles were implanted into the periphery of the cervical mass, eight 3.0 mg. needles in two vertical layers in the right parametrium and a long two section 25 mg. radium capsule was placed in the lower segment of the uterus for 7 days. Roentgen therapy was administered daily to two 15×15 cm. ports laid out over the anterior and posterior right pelvis at the rate of 200 r (air dose) per port until 6 treatments were given. The treatment factors were 200 kv., a target skin distance of 80 cm., a filter of 0.5 mm. of copper and 1.0 mm. of aluminum. At the end of 6 weeks this roentgen therapy was repeated, thereby bringing the dose per port to 2,400 r.

At 3 months she was almost free of pain and felt much better. There was a small patch of radiation reaction on the face of the cervix but no visible evidence of carcinoma could be detected and the parametrium was soft. At 5 months a urogram showed the right kidney pelvis to have a normal appearance. At 9 months she felt well but a defect in the right ureter suggested the retroperitoneal extension of cancer above the original treated area and another course of roentgen therapy, adding 2,000 r to each of the two ports over the right pelvis, was given in 12 days.

At 16 months the right leg was swollen as a result of lymphatic blockage produced by radiation fibrosis in the right groin. At 17 months a small patch of radiation reaction in the posterior bladder wall was treated successfully by a urologist. At 3 years and 4 months she developed pain in the right pelvis when she was on her feet and a roentgenographic examination revealed fracture lines through both rami of the right pubis. Another examination done 2 months later showed callus formation about the fractures and the pain had disappeared. At 5 years she had no discomfort but walked with some difficulty because of the persistent swelling of the right leg from groin fibrosis. Pelvic examination revealed no evidence of carcinoma and a urogram showed normal kidney pelves.

Calculations indicate that the total dose of roentgen rays given to the midplane of the right pelvis during the year of treatment amounted to approximately 5,000 r. This therapy produced no internal damage but caused an induration in the subcutaneous tissues of the right groin with secondary lymphatic blockage. In the light of our present knowledge we believe that the results would have been as good if the third course of roentgen treatments had been omitted, thereby eliminating excessive fibrosis in the groin and swelling of the leg.

## COMMENT

Since ureteral obstruction may be produced by external pressure as well as by direct invasion of the structures, it seems reasonable to assume that this complication might occasionally be relieved by conventional irradiation techniques. However, we have as yet been able to find very few such favorable results reported in the literature. Schewe[17] recently observed 5 cases that showed a disappearance of such strictures following roentgen therapy. A protracted series of intravaginal and external roentgen treatments was given to each case at the Ellis Fischel State Cancer Hospital during a period of 60 days. Three of these patients were living and well 9, 9 and 15 years later.

In a personal communication, Sherman states that he has seen similar results in a few of his cases treated with combinations of radium, roentgen rays, radioactive gold and surgery, but one finds it difficult to assign credit to the proper modality when such techniques are used.

## SUMMARY

Dog experiments and clinical experience indicate that stricture of normal ureters can be produced by relatively small amounts of beta radiation, whereas cancerocidal doses may be used safely near the

Fig. 5. Case v. Right sided hydronephrosis from malignant invasion of the parametrium (*A* and *B*) 5 months following the implantation of low intensity radium needles in the cervix and parametrium and insertion of a low intensity cervical capsule (*C*) for 7 days and the administration of conventional roentgen therapy to the right pelvis. (*D*) The urinary tract is still normal at the end of 5 years.

ureters when they are delivered as gamma rays emitted by low intensity interstitial sources. Cases are described in which ureteral strictures secondary to malignant parametrial invasion were caused to disappear by the implantation of low intensity radium needles in the parametria.

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# SURVIVAL IN INVASIVE CARCINOMA OF THE CERVIX FIVE TO TEN YEARS AFTER RADIATION THERAPY*

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ALTHOUGH the recent emphasis on early diagnosis of carcinoma of the cervix is commendable, it tends to obscure the fact that even advanced lesions may respond satisfactorily to treatment. It appears to be unnecessarily pessimistic to believe that further improvement in the salvage of patients with carcinoma of the cervix is impossible by the utilization of radiation or surgical procedures; this pessimism is unwarranted because (1) these are the only successful methods of treatment available for this condition at the present time and (2) further improvement in both techniques is entirely possible. Obviously, further basic research in the biology of cancer and new avenues of treatment are essential. It also appears, however, that a more thorough study of patients already treated might yield additional information. Most of the reported series of cases of cervical carcinoma are based on five year survival; some of the surgical literature includes even shorter periods of observation. However, now that therapeutic techniques have become somewhat stabilized, it is increasingly important to examine the causes of death after treatment following a survival interval of more than five years. Such studies are particularly informative in carcinoma of the breast.

It is the practice of those responsible for the Annual Report on the Results of Treatment in Cancer of the Uterus[1] to report results at periods of five, seven and ten years after treatment. Table 1 shows the five and ten year survival rates from four institutions referred to in the above report that are somewhat comparable to those of the Mayo Clinic regarding the volume of patients treated. Survival rates at five years have been reported from our series, but the ten year results have not been compiled previously.

TABLE I

SURVIVAL RATES IN CARCINOMA OF THE CERVIX TREATED AT VARIOUS LOCALITIES

| Locality | Patients Alive without Disease | | | |
|---|---|---|---|---|
| | Five Year Follow-up | | Ten Year Follow-up | |
| | No. | Per Cent | No. | Per Cent |
| Stockholm | 834 | 48.5 | 548 | 36.9 |
| Manchester | 665 | 39.4 | 480 | 29.6 |
| St. Louis | 228 | 55.6 | 60 | 30.3 |
| Copenhagen | 763 | 50.8 | 546 | 37.2 |

## SCOPE OF PRESENT STUDY

The patients reported on here include all those treated at the Mayo Clinic from 1940 through 1949. A previous report[3] described the five year survival of patients treated from 1940 through 1948, including many of those involved in the present study. However, all cases of noninvasive carcinoma of the cervix have been excluded from the present group. Also, a careful pathologic and clinical re-evaluation of all tumors has shown that some previously considered as Stage 1 lesions were actually carcinoma *in situ*, and they have been deleted from the

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Table II

CLASSIFICATION OF 1,300 CARCINOMAS OF THE CERVIX: MAYO CLINIC, 1940–1949

| Type of Lesion | Time of Treatment | | | |
|---|---|---|---|---|
| | 1940–1944 | | 1945–1949 | |
| | No. | Per Cent | No. | Per Cent |
| Squamous cell epithelioma | | | | |
| Stage I | 55 | 8.4 | 78 | 11.9 |
| Stage II | 152 | 23.5 | 191 | 29.3 |
| Stage III | 207 | 32.1 | 164 | 25.2 |
| Stage IV | 106 | 16.4 | 52 | 7.7 |
| Modified | 84 | 13.1 | 121 | 18.5 |
| Other carcinomas | 42 | 6.5 | 48 | 7.4 |
| Total | 646 | 100.0 | 654 | 100.0 |

present series. Table II shows the distribution of the present series according to stages of the lesions; the patients are divided into two main subgroups, namely, those treated from 1940 through 1944, and those treated from 1945 through 1949. The first subgroup numbered 646, and the second numbered 654, giving a total of 1,300 cases. The category designated as "modified" includes all patients in whom a definitive attempt at treatment of the cervical carcinoma, whether surgical or by radiation, had been made before we saw the patient. The group called "other carcinomas" includes adenocarcinoma, adenoacanthoma and hemangio-endothelioma (1 case).

It is extremely difficult to arrive at accurate staging of the lesions in the modified group of cases, but an attempt was always made to do this for the sake of our own comparative observations.

During the decade of 1940 through 1949, a definite shift occurred in lesions of the earlier stages. In the first five year period, 32 per cent of the lesions were Stage I or II; in the latter five years, 41 per cent were in this category. The more extensive lesions changed even more dramatically; Stage III and IV lesions from 1940 through 1944 comprised 49 per cent of the total, whereas only 33 per cent were in this category during the second half. The modified group increased from 13 to 19 per cent, which reflects the changing pattern of our particular practice in that more patients are being treated prior to examination at the clinic and, consequently, the percentage of complicated problems is increasing.

## TREATMENT

Table III shows the different forms and combinations of treatment utilized. Definitive radiation therapy was given to 1,143 patients. Surgical treatment alone or with postoperative irradiation was employed in the remaining 157 patients. The division

Table III

TREATMENT OF 1,300 CARCINOMAS OF THE CERVIX: MAYO CLINIC, 1940–1949

| Type of Treatment | Time of Treatment | | | |
|---|---|---|---|---|
| | 1940–1944 | | 1945–1949 | |
| | No. | Per Cent | No. | Per Cent |
| Radium alone | 48 | 7.4 | 51 | 7.8 |
| Roentgen rays alone | 16 | 2.5 | 35 | 5.4 |
| Radium and roentgen rays | 508 | 78.6 | 485 | 74.1 |
| Surgery alone | 17 | 2.7 | 37 | 5.6 |
| Surgery and radium | 2 | 0.3 | 2 | 0.3 |
| Surgery and roentgen rays | 30 | 4.6 | 22 | 3.4 |
| Surgery, radium and roentgen rays | 25 | 3.9 | 22 | 3.4 |
| Total | 646 | 100.0 | 654 | 100.0 |

of patients according to the type of treatment remained remarkably constant in the two five year periods. In the first period, 88 per cent received radiation therapy primarily and 12 per cent received surgical treatment primarily; these percentages in the second period were 87 and 13, respectively. Thus, there was no pronounced change in philosophy regarding the management of carcinoma of the cervix throughout this decade.

*Details of Therapeutic Technique.* The technical details of radiation therapy at the clinic vary somewhat from those of methods used elsewhere. Our technique has been described previously,[3] but a brief recapitulation is essential to the interpretation of the tables that follow.

A complete course of treatment for carcinoma of the cervix, carried out whenever cure appears to be possible, covers a period of about four weeks. Thorough general and pelvic examinations yield essential information regarding the physical status of the patient and the stage or extent of the tumor according to the international classification. Biopsy of the growth is always performed, and its malignancy is graded according to Broders' classification. In cases of carcinoma of Stage III or IV, excretory urograms and proctoscopic examinations are made.

Treatment is started with radium; roentgen or radiocobalt ($Co^{60}$) therapy is instituted within one or two days and continued concurrently with the radium therapy. The unit of radium is the 50 mg. tube filtered with 1 mm. of platinum. The active length of the tube is 11.7 mm. The over-all length is 19 mm. and the diameter is 4.0 mm. Because of this small diameter, dilatation of the cervix is avoided. Trauma is minimal, and good exposure of the cervix is obtained by having the patient assume the knee-chest position at every treatment with radium; the resultant expansion of the vagina with air affords space for packing with abundant amounts of gauze after insertion of the radium tube.

Applications of radium usually are made twice weekly for a period of four weeks throughout treatment. In the absence of complications, such as infection or hemorrhage, hospitalization is necessary only on the day and night of the radium treatments. In the two or three day interval between applications of radium, the patient is ambulatory. Being out of the hospital and up and around increases the strength and morale of the patient.

In the application of radium, an effort is made to obtain homogeneous irradiation along the entire birth canal. The 50 mg., platinum-filtered tube is placed in the proximal portion of the cervical canal for ten to fourteen hours at each of the first two treatments, the posterior vaginal wall being packed well away from the radium to secure protection of the rectum. In the third and fourth treatments, also of ten to fourteen hours each, the tube is placed in the middle or deeper part of the cervical canal.

Since cervical carcinoma frequently spreads through the internal os to involve the endometrium, a tandem is introduced into the uterine cavity at the fifth radium treatment, two 50 mg. tubes being used for a period of twenty to twenty-four hours. Roentgen therapy necessarily is omitted on this day. The last three treatments are given in the vaginal cavity, the 50 mg. tube being enclosed in a plastic cylinder of appropriate size. The cylinder used most frequently has a wall that is 1 cm. in thickness; it is placed transversely across the face of the cervix, then in the right vaginal fornix, and finally in the left vaginal fornix, for a treatment time of ten to fourteen hours in each locality.

Thus, a complete course of treatment for a small lesion in a patient with a small vaginal cavity would total about 5,500 mg. hours in four weeks; a bulky carcinoma would receive a minimum of 7,300 mg. hours. Point A would receive at least 7,000 gamma roentgens and point B would receive at least 2,000 gamma roentgens in a large tumor with full dosage.

All of the patients with whom this report is concerned were treated during the period

of 1940 through 1949, and the technique of roentgen therapy in the majority of instances differed from the present scheme. Treatment was administered after completion of the course of radium therapy. Two anterior and two posterior pelvic ports were treated, each of which measured approximately 15 by 15 cm.; there was no midline separation between adjacent fields. A total dose of 540 r (air) was administered to a single field daily, employing 200 kv. with a half value layer of 1.0 mm. of copper. The course of treatment was repeated after an interval of three months.

At the present time, roentgen therapy is administered to two anterior and two posterior pelvic ports, with midline protection between adjacent zones. Daily treatments of 200 r (air) are delivered at a distance of 50 or 70 cm. to each of two ports for a total dose of 2,000 to 2,400 r per port, employing 250 kv. with a half value layer of 1.3 mm. of copper. However, many patients receive cobalt 60 teletherapy, and a midplane pelvic tumor dose of 3,500 to 3,700 r is delivered.

After treatment, the patients are examined every three months during the first year. If satisfactory healing has occurred, they are seen twice during the second year and yearly thereafter. This method of treatment relies more on radium therapy than do many other techniques. The applications of radium take care of the entire uterus, and the roentgen or cobalt 60 teletherapy is relied on to supplement the radium in an effort to sterilize any spread of carcinoma into the lateral pelvic lymph nodes.

Some patients cannot be given the entire course of radiation. The most common reasons for limiting therapy are far-advanced disease, pelvic cellulitis or pronounced debility of the patient. Other generalized diseases may require modification of the treatment. Patients in whom the entire course of therapy could not be completed are listed in the following tables under "limited radiation therapy." All others are included under "complete radiation therapy."

## RESULTS

*Complete Radiation Therapy (1940–1944).* In the interval from 1940 through 1944, a total of 431 patients received complete radiation therapy (Table IV). The survival rate of the traced patients was 56 per cent after five years and 49 per cent after ten years. These data emphasize that extremely few Stage I lesions were treated by radiation in this interval, the majority of such lesions being treated surgically. The relatively excellent survival rate in each of the groups demonstrates the good general condition of the patients.

*Limited Radiation Therapy (1940–1944).* Table V indicates that 141 patients received limited radiation therapy during the first five year period. The five year survival rate was only 24 per cent, and the ten year survival rate was 19 per cent. Nearly half of the patients in this group were in the modified category, in which the rates were 23 and 13 per cent, respectively. Many of these patients obviously received benefit from further treatment, limited though it was.

Thus, from 1940 through 1944, a total of 572 patients received radiation therapy for carcinoma of the cervix, with a five year survival rate of 48 per cent and a ten year survival rate of 42 per cent.

*Complete Radiation Therapy (1945–1949).* A total of 403 patients received complete radiation therapy from 1945 through 1949 (Table VI). The number of Stage I lesions treated by radiation significantly increased during this second five year period as the result of two factors, namely, (1) more Stage I lesions were seen and (2) the number treated surgically decreased somewhat. The survival rate of the entire group of patients was 61 per cent for five years and 49 per cent for ten years, which is not remarkably different from the previous five year interval. The change in the number of Stage II lesions is noteworthy. A considerably larger group of patients with such lesions was seen in the latter part of the decade; a corresponding decrease in the total number of Stage III lesions occurred.

TABLE IV

SURVIVAL DATA AFTER COMPLETE RADIATION THERAPY FOR CARCINOMA OF THE CERVIX: MAYO CLINIC, 1940–1944

| Type of Lesion | Patients | | Lived Five or More Years after Treatment | | Patients | | Lived Ten or More Years after Treatment | |
|---|---|---|---|---|---|---|---|---|
| | Total | Traced | No. | Per Cent* | Total | Traced | No. | Per Cent* |
| Squamous cell epithelioma Stage I | 7 | 7 | 5 | 71.4 | 7 | 7 | 5 | 71.4 |
| Stage II | 137 | 132 | 105 | 79.5 | 137 | 132 | 95 | 72.0 |
| Stage III | 189 | 185 | 97 | 52.4 | 189 | 182 | 82 | 45.1 |
| Stage IV | 62 | 61 | 16 | 26.2 | 62 | 61 | 13 | 21.3 |
| Modified | 15 | 13 | 2 | 15.4 | 15 | 13 | 1 | 7.7 |
| Other carcinomas | 21 | 19 | 8 | 42.1 | 21 | 19 | 7 | 36.8 |
| Total | 431 | 417 | 233 | 55.9 | 431 | 414 | 203 | 49.0 |

* Based on traced patients. Inquiry as of January 1, 1960.

TABLE V

SURVIVAL DATA AFTER LIMITED RADIATION THERAPY FOR CARCINOMA OF THE CERVIX: MAYO CLINIC, 1940–1944

| Type of Lesion | Patients | | Lived Five or More Years after Treatment | | Patients | | Lived Ten or More Years after Treatment | |
|---|---|---|---|---|---|---|---|---|
| | Total | Traced | No. | Per Cent* | Total | Traced | No. | Per Cent* |
| Squamous cell epithelioma Stage I | 2 | 2 | 1 | 50.0 | 2 | 2 | 1 | 50.0 |
| Stage II | 8 | 8 | 6 | 75.0 | 8 | 8 | 6 | 75.0 |
| Stage III | 14 | 14 | 7 | 50.0 | 14 | 14 | 6 | 42.9 |
| Stage IV | 38 | 38 | 2 | 5.3 | 38 | 38 | 2 | 5.3 |
| Modified | 69 | 62 | 14 | 22.6 | 69 | 62 | 8 | 12.9 |
| Other carcinomas | 10 | 8 | 2 | 25.0 | 10 | 8 | 2 | 25.0 |
| Total | 141 | 132 | 32 | 24.2 | 141 | 132 | 25 | 18.9 |

* Based on traced patients. Inquiry as of January 1, 1960.

TABLE VI

SURVIVAL DATA AFTER COMPLETE RADIATION THERAPY FOR CARCINOMA OF THE CERVIX: MAYO CLINIC, 1945–1949

| Type of Lesion | Patients | | Lived Five or More Years after Treatment | | Patients | | Lived Ten or More Years after Treatment | |
|---|---|---|---|---|---|---|---|---|
| | Total | Traced | No. | Per Cent* | Total | Traced | No. | Per Cent* |
| Squamous cell epithelioma | | | | | | | | |
| Stage I | 31 | 30 | 27 | 90.0 | 31 | 29 | 24 | 82.8 |
| Stage II | 168 | 164 | 112 | 68.3 | 168 | 146 | 85 | 58.2 |
| Stage III | 132 | 132 | 68 | 51.5 | 132 | 119 | 45 | 37.8 |
| Stage IV | 34 | 32 | 15 | 47.0 | 34 | 31 | 13 | 41.9 |
| Modified | 19 | 18 | 8 | 44.4 | 19 | 18 | 1 | 5.6 |
| Other carcinomas | 19 | 18 | 9 | 50.0 | 19 | 17 | 7 | 41.2 |
| Total | 403 | 394 | 239 | 60.7 | 403 | 360 | 175 | 48.6 |

* Based on traced patients. Inquiry as of January 1, 1960.

This can only be explained by the earlier recognition and treatment of the disease, since few of these patients were treated surgically in either interval.

*Limited Radiation Therapy (1945–1949).* A total of 168 patients received limited radiation therapy in the interval from 1945 through 1949, with five and ten year survival rates of 24 and 11 per cent, respectively (Table VII). A discouraging note with this group is the pronounced increase in the so-called modified group. This reflects the fact that more localities from which our practice derives are providing radiation therapy or attempting radical surgical procedures than formerly and that more patients who have resistant or poorly responding lesions come to the clinic for treatment. The salvage rate in these patients is necessarily far less than it is in those treated primarily.

*All Types of Radiation Therapy (1940–1949).* Table VIII is a composite of the four preceding tables summarizing all patients treated from 1940 through 1949. The total of 1,143 patients had five and ten year survival rates of 49 and 40 per cent, respectively. A total of 40 patients (3.5 per cent) were lost to follow-up in five years, with 79 patients (7 per cent) lost to follow-up in ten years. These therapeutic results are not too dissimilar from the figures reported by the four other medical centers shown in Table I. They indicate ample room for improvement not only by the introduction of new techniques but also by further education of the public and meticulous application of the methods now available.

*Deaths.* Table IX shows the number of traced patients who died between five and ten years after treatment with radiation. This excludes deaths in patients whose lesions were modified by previous treatment, who had lesions other than squamous cell epithelioma, or who did not receive the complete course of radiation therapy. The greatest number of deaths occurred in the sixth year after treatment. The great majority of deaths were in patients with Stage II or III lesions. This is to be expected, since Stage I lesions that have been controlled for five years should remain so,

TABLE VII

SURVIVAL DATA AFTER LIMITED RADIATION THERAPY FOR CARCINOMA OF THE CERVIX: MAYO CLINIC, 1945–1949

| Type of Lesion | Patients | | Lived Five or More Years after Treatment | | Patients | | Lived Ten or More Years after Treatment | |
|---|---|---|---|---|---|---|---|---|
| | Total | Traced | No. | Per Cent* | Total | Traced | No. | Per Cent* |
| Squamous cell epithelioma Stage I | 2 | 2 | 1 | 50.0 | 2 | 1 | 0 | 0 |
| Stage II | 12 | 12 | 7 | 58.3 | 12 | 11 | 4 | 36.4 |
| Stage III | 22 | 21 | 10 | 47.6 | 22 | 21 | 7 | 33.3 |
| Stage IV | 22 | 22 | 2 | 9.1 | 22 | 22 | 0 | 0 |
| Modified | 96 | 90 | 15 | 16.7 | 96 | 90 | 4 | 4.4 |
| Other carcinomas | 14 | 13 | 3 | 23.1 | 14 | 13 | 3 | 23.1 |
| Total | 168 | 160 | 38 | 23.8 | 168 | 158 | 18 | 11.4 |

* Based on traced patients. Inquiry as of January 1, 1960.

TABLE VIII

SURVIVAL DATA AFTER ALL TYPES OF RADIATION THERAPY FOR CARCINOMA OF THE CERVIX: MAYO CLINIC, 1940–1949

| Type of Lesion | Patients | | Lived Five or More Years after Treatment | | Patients | | Lived Ten or More Years after Treatment | |
|---|---|---|---|---|---|---|---|---|
| | Total | Traced | No. | Per Cent* | Total | Traced | No. | Per Cent* |
| Squamous cell epithelioma Stage I | 42 | 41 | 34 | 82.9 | 42 | 39 | 30 | 76.9 |
| Stage II | 325 | 316 | 230 | 72.8 | 325 | 297 | 190 | 64.0 |
| Stage III | 357 | 352 | 182 | 51.7 | 357 | 336 | 140 | 41.7 |
| Stage IV | 156 | 153 | 35 | 22.9 | 156 | 152 | 28 | 18.4 |
| Modified | 199 | 183 | 39 | 21.3 | 199 | 183 | 14 | 7.7 |
| Other carcinomas | 64 | 58 | 22 | 37.9 | 64 | 57 | 19 | 33.3 |
| Total | 1,143 | 1,103 | 542 | 49.1 | 1,143 | 1,064 | 421 | 39.6 |

* Based on traced patients. Inquiry as of January 1, 1960.

TABLE IX

NUMBER OF DEATHS* FIVE TO TEN YEARS AFTER COMPLETE RADIATION THERAPY FOR CARCINOMA OF THE CERVIX

| Type of Lesion | Year after Radiation | | | | | Total |
|---|---|---|---|---|---|---|
| | 6th | 7th | 8th | 9th | 10th | |
| Squamous cell epithelioma Stage I | 0 | 0 | 2 | 0 | 0 | 2 |
| Stage II | 7 | 3 | 3 | 3 | 5 | 21 |
| Stage III | 9 | 4 | 4 | 6 | 3 | 26 |
| Stage IV | 3 | 2 | 0 | 2 | 0 | 7 |
| Total | 19 | 9 | 9 | 11 | 8 | 56 |

* This excludes patients whose lesions were modified by previous treatment elsewhere or who had lesions other than squamous cell epithelioma.

and the vast majority of patients with Stage IV lesions are already dead. Van Herik and Fricke[5] noted a steady decrease in the incidence of recurrence from the time of treatment to the fifth year, and this apparently occurs also in the interval from five to ten years. Table X is an attempt to classify the deaths between five and ten years on the basis of metastasis or recurrence, or the presence of other diseases. This is particularly difficult in our type of practice, because many patients come from a distance and the terminal phases are observed by the home physician. As far as can be determined, 32 of the 56 deaths during this period resulted from recurrent or metastatic carcinoma of the cervix and 8 patients died from other causes, such as a cerebrovascular accident or cardiac disease; in the remaining 16 cases, not enough information was available to allow accurate determination of the cause of death.

## COMMENT

According to Miller and associates,[4] the basic concepts of the treatment of carcinoma of the cervix remain in a "polemic groove, oscillating between irradiation and surgery." Our associates and we have attempted to avoid this by the team approach to a decision regarding treatment. With few exceptions, all of the patients in this series were seen and evaluated by a gynecologist, a radiation therapist and a surgeon, and then the decision was made as to the best type of treatment for the individual patient. This approach has merit but is by no means infallible, since human error cannot be so easily eliminated.

TABLE X

CAUSE OF DEATH* FIVE TO TEN YEARS AFTER COMPLETE RADIATION THERAPY FOR CARCINOMA OF THE CERVIX

| Type of Lesion | Cause of Death | | | Total |
|---|---|---|---|---|
| | Recurrent or Metastatic Carcinoma | Disease Other Than Carcinoma of Cervix | Unknown | |
| Squamous cell epithelioma Stage I | 1 | 0 | 1 | 2 |
| Stage II | 9 | 6 | 6 | 21 |
| Stage III | 18 | 2 | 6 | 26 |
| Stage IV | 4 | | 3 | 7 |
| Total | 32 | 8 | 16 | 56 |

* This excludes the same patients as in Table IX.

When the results of therapy in the decade under consideration were divided into two five year intervals a significant trend could be seen in the second interval toward earlier recognition and treatment of the disease. It is hoped, and the clinical impression supports this view, that this trend has continued. At the same time, however, an increased number of patients were seen with lesions whose course had been modified by previous treatment that, in many instances, was incomplete according to the best standards. The low rate of salvage in such patients has been emphasized.

Much information is bound to be forthcoming from studies such as those recently initiated by Cosbie[2] in which the patients have been observed from the time of treatment to their death. The nature of the source of our patients makes it difficult to pursue such a program at our institution, but attempts are current to follow our treated patients more systematically than heretofore has been the rule. Determination of the five year survival rate is more important in carcinoma of the cervix than it is in many other tumors, but much valuable information will be lost if the follow-up is terminated at this point.

## SUMMARY AND CONCLUSIONS

The 1,300 patients included in this report comprise all those treated for carcinoma of the cervix at the Mayo Clinic from 1940 through 1949. Definitive radiation therapy was given to 1,143 patients, and 157 patients were treated primarily by surgical techniques.

The over-all survival rate for the 1,143 patients who received definitive radiation therapy was 49 per cent for five years and 40 per cent for ten years. If all the patients lost to follow-up were considered to have died of carcinoma of the cervix, the survival rate would be 47 per cent for five years and 37 per cent for ten years.

Of the 56 patients with squamous cell epithelioma of the cervix treated primarily at the clinic who died between five and ten years after treatment, 32 died of recurrent or metastatic carcinoma of the cervix and 8 died of other diseases; not enough information was available in the remaining 16 cases to determine the cause of death.

A plea is made for long-term follow-up on all patients with carcinoma of the cervix in the hope that such retrospective studies may add to knowledge of the nature and behavior of this malignant tumor after treatment.

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VOL. 85, NO. 3

# ENDOMETRIAL CARCINOMA*

## A THIRTEEN YEAR REVIEW

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THERE is a growing mass of evidence indicating that the incidence of carcinoma of the uterine fundus is approaching the incidence of carcinoma of the uterine cervix.[4,14,15,17,25] Better diagnostic methods, an increased awareness on the part of both patient and physician and the advancing age of the population are accepted as the explanation for this phenomenon. Since 1956, when the Oklahoma Hospitals began compiling records, 2.3 per cent of all cancer admissions have been patients with endometrial carcinoma. At this institution, fundal cancer is diagnosed as frequently as carcinoma of the urinary bladder and carcinoma of the rectum.

### MATERIAL AND CLINICAL FINDINGS

Eighty-three women were treated for endometrial carcinoma in the University of Oklahoma Hospitals from March, 1945, to March, 1958, a thirteen year period. A statistical analysis of 82 of these patients is the basis of the present study. One patient has been lost to follow-up and is not included. Almost all the women were clinic patients and have been followed in the University Clinic's outpatient department. There were only 7 private patients and they were traced without difficulty by contacting the referring physician. The five year salvage rate is based on 50 patients treated prior to March, 1955.

Pertinent vital statistics of the 82 patients are summarized in Table I. Seventy-three were married; 22 were childless. The association of corpus cancer with sterility has been established for many years.[25,30] The significance of this relative increase with childlessness is not as yet fully understood. The average age of the patients was fifty-eight years. It is interesting to note that 84 per cent of our cases occurred after the age of fifty. The youngest woman was thirty-two, the oldest eighty-six. Of the group, 78 per cent were postmenopausal. The predisposition of this malignancy for women whose menses have ceased has been repeatedly stressed in the literature.[1,9,24,29]

Figure 1 indicates the grave significance of postmenopausal bleeding. In our series, the complaints ranged from seemingly innocuous intermenstrual spotting to sudden onset of vaginal hemorrhage many years after cessation of menses. It is apparent that postmenopausal bleeding, however slight, must be considered a manifestation of gynecologic cancer until proved otherwise by means of diagnostic dilatation and curettage. The only other symptom described with any degree of regularity was abdominal discomfort of varying nature.

For many years there has been an attempt to correlate endocrine abnormalities with the development of adenocarcinoma of the uterus.[2,6,9,17,33,34] The interrelationship of endometrial hyperplasia, hyperestrogenism and aberration of carbohydrate metabolism has been investigated extensively in the British literature.[19,30] These studies have demonstrated an abnormal incidence of benign glandular hyperplasia in patients with frank diabetes and patients with high glucose tolerance curves who are not clinically diabetic. By inference, a qualitative and quantitative relationship is assumed between hyperactivity of the anterior pituitary gland and corpus cancer. In 1935, Stein and Leventhal[31] described the syndrome which bears their name and noted that such cases were more prone to develop endometrial carcinoma than could be explained on the basis of chance. They surmised that some abnormality of the pituitary-adrenal-ovarian balance was responsible.

The endocrinopathies observed in our series are summarized in Table II: 57 were

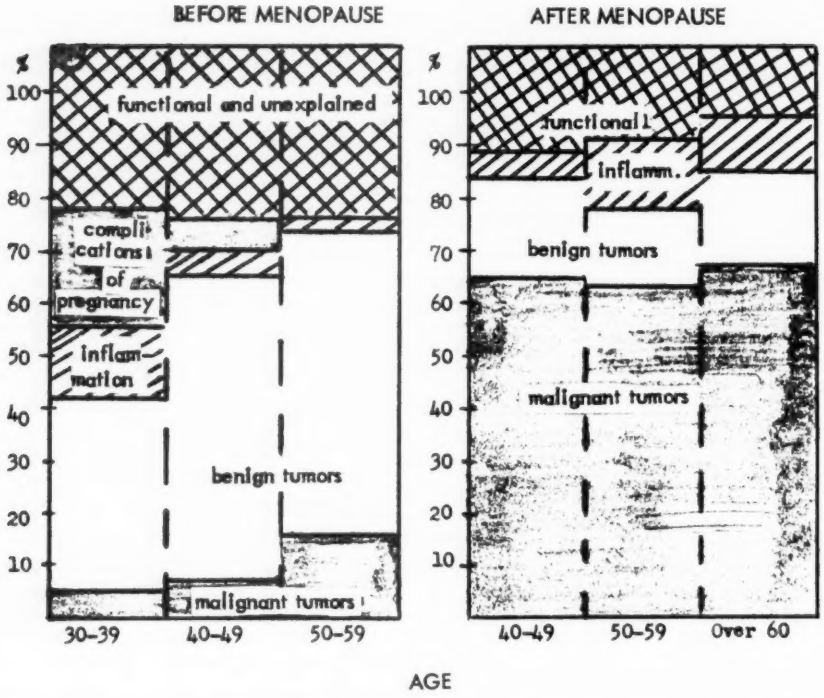


FIG. 1. Relative frequency of causes of gynecologic bleeding. Graphic evidence of the serious implication of vaginal bleeding in the postmenopausal patient. (Modified from Taylor and Millen.[34])

described as obese; 24 menstruated beyond the age of 50; 36 were definitely hypertensive with diastolic pressures of at least 100; and 13 had a clinical diagnosis of diabetes. It is noted that 12 patients presented the triad of diabetes, hypertension and obesity.

TABLE I

VITAL STATISTICS OF 82 PATIENTS WITH ENDOMETRIAL CANCER

| | |
|---|---|
| Marital Status | 90% married |
| Age | Range from 32–86<br>66% from 50–65<br>Average age 58 |
| Parity | 24% childless |
| Race | 83% white |
| Economic Status | 90% charity |
| Menopause | 78% postmenopausal<br>Average age at menopause 47 |
| Symptoms | Vaginal bleeding 98%<br>Abdominal pain 33% |

In this series, the staging system set forth in the Stockholm League of Nations report[32] has been used. Stage I refers to cancer clinically confined to the uterus. Stage II includes cancer which has spread beyond the confines of the uterus, based on palpation of an irregular extrauterine mass, obvious invasion of surrounding tissue, and/or evident metastases. Of our patients,

TABLE II

ENDOCRINOPATHIES OBSERVED IN 82 PATIENTS WITH ENDOMETRIAL CANCER

| Abnormality | No. of Cases | Per Cent | Per Cent of General Population |
|---|---|---|---|
| Obesity | 57 | 70 | 40 |
| Menopause after Age 50 | 24 | 40 | 8–15 |
| Nulliparity | 20 | 24 | 15–16 |
| Hypertension | 36 | 44 | 25–30 |
| Diabetes | 13 | 16 | 1 |
| Ovarian Neoplasm | 2 | 2.4 | — |
| Hypertension, Diabetes and Obesity | 12 | 14.6 | — |

77 per cent were classified as Stage I; 23 per cent as Stage II. Unavoidable errors in classification are inherent in this staging system, since clinical criteria alone are utilized. In retrospect, it can be assumed that most of the Stage I patients who died of progressive disease were undetected Stage II cases at the time of treatment.

Histologic diagnoses are available in all cases. Adenocarcinoma was reported in 78 patients and adenoacanthoma in 4. No attempt has been made to classify the neoplasms according to histologic grade.

## TREATMENT

During the thirteen years covered by this study, several modes of therapy have been used. No fixed plan of treatment has evolved. Of the 82 cases, 36 were treated by surgery plus some form of irradiation; 29 patients underwent hysterectomy alone, receiving no other definitive therapy; and 17 were treated by irradiation alone.

In respect to comparison of modalities, the number of cases is too small and is so affected by selection that no statistically valid conclusions can be drawn. From the data available, however, some generalizations can be made. Apparently, individual selection has resulted in the use of surgery, either alone or in conjunction with irradiation, in good risk, Stage I patients. Irradiation alone has been used primarily to palliate poor risk, debilitated patients. Contraindications to surgery have included far advanced local malignancy, extreme obesity, metastatic cancer and systemic cardiovascular disease.

An evaluation of the type of radiation therapy which was administered is important. Most of the patients who were not surgical candidates were treated by a single radium application. A metal tandem containing 50–75 mg. of radium was inserted into the endometrial cavity and allowed to remain for 3,000–5,000 mg. hours. Occasionally, vaginal colpostats were utilized as an adjunct. The radium application was not followed by external roentgen therapy unless persistent or recurrent disease necessitated further treatment. When intrauterine radium was impracticable, the patient was treated by orthovoltage external roentgen therapy. The dosage varied, usually two anterior and two posterior fields were carried to skin tolerance. This approach to radiation therapy bears little relationship to the thorough, painstaking therapeutic program described by Heyman.[12,13] Therefore, it can be assumed that no patient received what is now accepted as a full course of irradiation. It is surprising and gratifying that some of the Stage I patients who were considered poor surgical candidates have been salvaged by irradiation alone.

It is interesting to note that the radium technique and dosage were essentially the same whether or not the irradiation was to be followed by surgery. Of the 36 patients who were treated by a combined approach, 27 received preoperative radium therapy delivered by tandem or needles. Nine women had far advanced local cancer, which precluded a radium application; therefore, external therapy was given prior to surgery.

## RESULTS

The results of treatment according to the type of therapy and stage of the disease are shown in Table III. Apparent cures include patients who are alive and well at least two years following treatment and those who have died of intercurrent disease unrelated to uterine cancer. Thus, 61 of the 82 patients (74.4 per cent) represent apparent cures. Since 5 patients have died of unrelated causes, the absolute cure rate, then, is 56 of 82 (68.3 per cent).

Fifty patients have been followed at least five years. Twenty-nine are living and well, an absolute salvage of 58 per cent. Since 4 of these patients have died of intercurrent disease, the apparent five year survival rate is 67 per cent. Results of treatment elsewhere are summarized in Table IV.

As indicated in Table III, the major factor in ultimate prognosis is the stage of the disease at the time of diagnosis and

TABLE III

RESULTS OF TREATMENT IN 82 PATIENTS WITH ENDOMETRIAL CANCER ACCORDING TO STAGE OF THE DISEASE AND TYPE OF THERAPY

| Type of Therapy | Stage I | | | Stage II | | |
|---|---|---|---|---|---|---|
| | Total No. of Cases | Apparent Cures | | Total No. of Cases | Apparent Cures | |
| | | No. of Cases | Per Cent | | No. of Cases | Per Cent |
| Surgery Alone | 27 | 27 | 100 | 2 | 1 | 50 |
| Irradiation Plus Surgery | 28 | 26 | 95 | 8 | 3 | 38 |
| Radium Alone* | 4 | 2 | 50 | 2 | 0 | — |
| Roentgen Rays Alone* | 4 | 2 | 50 | 7 | 0 | — |
| Total | 63 | 57 | 90.5 | 19 | 4 | 21 |

* Incomplete course of irradiation by present day standards; not suitable patients for surgery.

treatment. Gratifying results can be expected in patients with cancer clinically confined to the uterus. Of the 55 Stage I cases receiving definitive treatment, only 2 are classified as treatment failures. It is significant that 4 of the 8 Stage I patients not considered surgical candidates and treated by less than optimal irradiation are living without cancer at this time.

Patients with Stage II lesions have a poor prognosis. In this series, only 3 of 19 patients have survived. One patient died in congestive heart failure four years after treatment and 15 must be classified as treatment failures. Similarly discouraging results have been reported from other institutions; the usual salvage rate in Stage II patients averages 15–20 per cent.[14,22]

TABLE IV

SUMMARY OF REPORTED RESULTS

| Treatment | No. of Cases | Five Year Survival (per cent) |
|---|---|---|
| *Preoperative Irradiation* | | |
| Heyman[12,13] | 65 | 78 |
| Rhode Island Hospital[3] | 67 | 61 |
| Hundley *et al.*[14] | 81 | 84 |
| *Radium Alone* | | |
| Heyman[12,13] | 459 | 62 |
| Rhode Island Hospital[3] | 28 | 43 |
| Corscaden[3] | 27 | 48 |
| *Hysterectomy Alone* | | |
| Rhode Island Hospital[3] | 22 | 68 |
| Arneson[1] | 18 | 84 |
| Masson[3] | 306 | 67 |
| Finn[8] | 39 | 70 |

## DISCUSSION

The literature on the treatment of endometrial carcinoma is quite voluminous. General surgeons, radiologists, gynecologists, and other members of the medical profession have expressed their individual and collective views for many years. As yet, no unanimity of opinion is available. Certain premises are generally accepted:

1. The diagnosis should be established histopathologically prior to any treatment.
2. The best results are obtained when a hysterectomy is practicable.
3. The results are considerably improved by judicious radiation therapy, preferably preoperative.
4. A coordinated approach utilizing the resources of the gynecologist and the radiologist is necessary, and it must include diagnosis, treatment, and follow-up care.

The superiority of a combined therapeutic approach is not universally accepted. Heyman,[13] who has had as much experience with corpus cancer as any physician in the world, believes that radiation therapy should be the primary treatment and surgery is to be performed only if uncontrolled disease persists. Conversely, some authorities[28,30] advocate immediate hysterectomy to be followed by radiation therapy in cases

Table V

COMPARISON OF REFORTED FIVE YEAR SURVIVAL RATES FOR ENDOMETRIAL CANCER TREATED BY SURGERY ALONE AND BY IRRADIATION FOLLOWED BY SURGERY

| Author | Surgery (per cent) | Irradiation Followed by Hysterectomy (per cent) |
|---|---|---|
| Arneson[1] | 79 | 87 |
| Cosbie *et al.*[5] | 73 | 85 |
| Payne[23] | 80 | 93 |
| Randall, Mirick, and Wieben[26] | 62 | 82 |
| Randall and Goddard[25] | 60 | 76 |
| Schmitz *et al.*[29] | 79 | 90 |

of recurrent cancer.

Intrauterine placement of radium provides an effective control of the primary neoplasm and also delivers significant dosage to the parametrial tissues and the vaginal vault. An increased incidence of recurrence in the vaginal cuff is a major disadvantage of the use of surgery alone.[15,17] Several investigators have published salvage rates for surgery as compared to their results with combined irradiation and surgery (Table v). As a result of their studies, they have become champions of combined treatment.[4,5,14,16,22,23,26] Optimum preoperative radium treatment eradicates histologic evidence of cancer in 60–90 per cent of operative specimens.[1,10,15,28] In our series, no malignant cells were identified in 71 per cent of the uteri which had been treated by radium prior to surgery.

Most authorities recommend that surgery follow irradiation within four to six weeks if at all possible.[14,34] Primary radiation therapy without subsequent surgery is advised only in cases made inoperable by nonresectability, severe systemic disease, and refusal of the patient to undergo the operation.

At the present time, most therapists utilize a technique whereby the uterine cavity is packed with multiple small sources of radium.[3,15,17,33,34] This procedure delivers a relatively homogeneous dosage of irradiation to all segments of the endometrium. Additional radium in the vaginal vault is aimed at preventing recurrence in this region. (Only 1 patient in this series was treated by the multiple capsule method, but during the past two years this technique has been used more frequently.) In some centers, supervoltage roentgen therapy has proved effective, especially in inoperable patients with extensive pelvic disease which precludes radium application.

## SUMMARY

Eighty-two patients treated for endometrial carcinoma at the University of Oklahoma Hospitals from 1945–1958 are reviewed. All of the patients have been followed for at least two years and 50 of these comprise the five year group. Fifty-six patients are living and well (68.3 per cent). The absolute survival rate in the patients followed five or more years is 58 per cent.

The grave significance of postmenopausal vaginal bleeding is emphasized. A diagnostic dilatation and curettage is imperative in all women who present with this complaint. The index of suspicion should be especially high in patients with various endocrinopathies, such as those evidenced by hypertension, benign endometrial hyperplasia, obesity, and diabetes.

The most important factor in ultimate survival is the stage of the disease at the time of diagnosis and treatment. The prognosis is excellent in cases in which the cancer is still clinically confined to the uterus.

When endometrial carcinoma is present, the treatment of choice is preoperative radium application followed by complete abdominal hysterectomy.

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# INCIDENCE OF PELVIC MALIGNANCIES FOLLOWING IRRADIATION FOR BENIGN GYNECOLOGIC CONDITIONS*

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CRITICAL reviews of the late results of the use of radiation therapy in benign conditions are in order because of the variable incidence of subsequent carcinogenesis reported by many authors. Procedures once considered routine, such as thymic irradiation of children with widened mediastinal shadows and spinal irradiation of adult males with rheumatoid spondylitis, have been largely abandoned in the past decade. The value of any form of therapy depends upon its success initially and its complications and death rate subsequently. It is generally agreed that any significant development of malignancy must be carefully weighed when radiation therapy is considered for benign lesions.

The incidence of pelvic malignancies following the use of radium and external irradiation in benign gynecologic conditions has been intensively reported in the gynecologic literature with virtual exclusion in radiologic journals. Until 1956, no report presented unequivocal evidence that irradiation for benign uterine bleeding predisposed to the subsequent development of pelvic neoplasia. Palmer and Spratt[15] found a 6.6 per cent incidence of late genital cancers in their series at Roswell Park Memorial Hospital, higher than that reported by any other author, and stated that "previous irradiation is, at least in part, responsible for subsequent malignancy." As these authors have noted, there are numerous pitfalls which may invalidate such a study. Before evaluating the different facets of the present survey, a review of the literature is in order to help define the issues more clearly.

## REVIEW OF THE LITERATURE

Previous studies exploring the problem of cancer induction following pelvic irradiation for gynecologic diseases of a benign nature have been along two lines: (1) the prospective approach, in which patients irradiated for benign bleeding have been followed for various periods to determine what percentage developed pelvic cancers; and (2) the retrospective approach, in which patients with gynecologic cancers have been studied to determine the percentage previously irradiated for benign lesions.

As early as 1925, Werner[22] noted an incidence of 0.3 per cent of gynecologic cancer in 2,680 patients subsequent to radiation therapy for menstrual disorders. A year later, in 1926, Vogt[21] substantiated this finding with a 0.4 per cent occurrence rate of endometrial carcinoma in 1,300 patients treated by radiation as opposed to a 5 per cent incidence of fundal carcinoma in all patients with menopausal bleeding. He concluded that radium therapy was protective in that the rate of malignancy was decreased by a factor of ten.

A case report of endometrial carcinoma seven years following roentgen-ray induced menopause was recorded by Macfarlane[10] in 1932 with a review of the literature to 1915. A total of 29 cases in seven articles, all in the German literature, was analyzed. The author concluded, "it is evident that the possibility of developing carcinoma in the uterus after radiation is very remote."

In 1934, Schmitz[18] found only 1 case of malignancy in 578 patients treated by ir-

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TABLE I

REVIEW OF THE LITERATURE

| Author | Year | No. of Cases | Cases Followed | | Interval (yr.) | Gynecologic Malignancies | |
|---|---|---|---|---|---|---|---|
| | | | No. | Per Cent | | No. | Per Cent |
| Schmitz[18] | 1934 | 578 | 578 | 100 | 6 (av.) | 1 | 0.17 |
| Costolow[2] | 1941 | 1,009 | 986 | 98 | 2.5–12.5 | 4 | 0.40 |
| Corscaden *et al.*[1] | 1946 | 1,100 | 958 | 88 | 6.7 (av.) | 17 | 1.90 |
| Crossen and Crossen[3] | 1947 | 526 | 526 | 100 | 5 (av.) | 5 | 0.95 |
| Montgomery *et al.*[12] | 1952 | 1,232 | 831 | 69 | 0.5–21 | 12 | 1.40 |
| Hunter *et al.*[8] | 1954 | 765 | 644 | 84 | 5 –20 | 3 | 0.50 |
| Palmer and Spratt[15] | 1956 | 1,670 | 721 | 43 | 10 –20 | 51 | 6.60 |
| Stander[19] | 1957 | 964 | 735 | 76.5 | 10 –24 | 19 | 2.60 |
| Rubin *et al.* | 1960 | 489 | 310 | 64 | 5 –33 | 7 | 2.20 |

radiation for benign uterine lesious (Table 1) and he questioned the role of radium in the cited case since atypia had been noted in the histologic sections eighteen months earlier. Later in the thirties, isolated instances of 1 or 2 cases of malignancy after irradiation of the uterus were described by Strachan,[20] Malpas,[11] Essen-Moller, and Luker[9] in the British literature.

In the forties, a number of larger series was reported (Table 1). In 1941, Costolow,[2] analyzing 1,009 cases of uterine fibroids treated by radium, found 4 cases of malignancy for an incidence of 0.4 per cent. Scheffey[17] a year later added 20 cases to the 71 so far reported of malignancy subsequent to irradiation of the uterus for benign conditions. Although he is often referred to as the first author implicating irradiation as a cause of the cancer, he concludes his paper with a statement of the opposite point of view, "errors of omission, either in technique or in judgment . . . not the radiation therapy itself, were the responsible factors in the subsequent occurrence of malignancy."

Corscaden *et al.*[1] in 1946 carefully reviewed their series and found 22 cases of pelvic neoplasia of which 18 were gynecologic in origin, representing a 1.9 per cent incidence rate. They expressed the opinion that the abnormal bleeding rather than irradiation was responsible for the malignancies. Crossen and Crossen[3] in the *only* controlled study showed that irradiation of uterine fibroids reduced the incidence of ovarian cancer and endometrial carcinoma. Thus, in 2,136 cases of nonirradiated myomas there were 13 cases of ovarian cancer (0.68 per cent) and 37 cases of fundal cancer (1.7 per cent) as opposed to an incidence in 526 cases of irradiated myomas of 1 case (0.19 per cent) of ovarian cancer and 4 cases (0.7 per cent) of fundal cancer.

In 1952, Montgomery *et al.*[12] found 12 cases of pelvic cancer in 831 cases of benign uterine bleeding treated by radium. Comparing the mortality and morbidity of surgery with the 1.4 per cent incidence of malignancy after utilization of radiation techniques, they concluded that the risk of radium therapy is very small and is to be preferred. Healy, in discussing this report, also felt that no relationship between irradiation and the late development of uterine carcinoma and sarcoma existed. Hunter *et al.*,[8] in 1954, presented a critical twenty year survey of their experience in the use of radium for the treatment of benign uterine lesions. After finding 3 late cases of gynecologic malignancies in 644 patients, they concluded, "an alleged high incidence of post-irradiation malignancy . . . has never been demonstrated by an analysis of actual clinical experience."

In 1956, Palmer and Spratt[15] sent questionaires to 1,670 patients treated with radium and roentgen rays for benign

uterine abnormalities. As mentioned, they found an unusually high incidence (6.6 per cent) of late malignancies compared to other authors. This they felt was due to the long follow-up (more than ten years) in their study; however, no mention was made of the fact that they had one of the lowest response rates in the literature with only 43 per cent of the patients answering and the consequent deletion of more than half of their series.

A comparable but much more complete experience was offered by Stander[19] in 1957 from the University of Michigan. In a study encompassing 964 patients who had radiation castration, 735 (76.5 per cent) were traced from ten to twenty-four years (average 16.6 years). There were 19 gynecologic cancers found for an incidence of 2.6 per cent, with endometrial carcinoma being the major group (14 cases). The author felt that the irradiation was not carcinogenic in pelvic structures and that the increased occurrence of endometrial carcinoma was due to endocrine abnormalities. Since the same control group was used in this series as in the Palmer and Spratt report,[15] one readily observes the conflicting and confusing nature of this survey of the literature.

## MATERIAL

### BENIGN GYNECOLOGIC CONDITIONS IRRADIATED

From 1927 to 1958, there were 469 cases of benign gynecologic conditions in our series which were irradiated by means of roentgen rays and radium. In Table II, the various disorders are listed. The majority of the lesions treated (68.2 per cent) were in those patients presenting with profuse and irregular menopausal and postmenopausal vaginal bleeding. Endometrial hyperplasia, histologically proved, constituted the largest single group, or 60 per cent, of the series. Curiously, myomata comprised only 13 per cent. Other reasons for irradiation such as endometriosis, sterilization, infections and infertility accounted for a relatively small percentage of the series. Beneficial results occurred in more than 90 per cent of these cases, as has been noted in similar instances by many authors.[1,12]

TABLE II

BENIGN GYNECOLOGIC CONDITIONS IRRADIATED 1927–1958 (469 CASES)

| | No. of Cases | Per Cent |
|---|---|---|
| Endometrial Hyperplasia (histologically proved) | 287 | 60 |
| Excessive Uterine Bleeding (histologically normal) | 86 | 17 |
| Myomata Uteri | 48 | 13 |
| Endometriosis | 16 | 3 |
| Cervicitis | 9 | 1.8 |
| Sterilization for Various Reasons (anemia, psychiatric conditions) | 9 | 1.8 |
| Excessive Uterine Bleeding (no histology) | 6 | 1.2 |
| Infections | 4 | 0.8 |
| Infertility | 2 | 0.4 |
| Pruritus Vulvae | 2 | 0.4 |

In reviewing the distribution of cases (Fig. 1), it was found that radium insertion for endometrial hyperplasia was done most frequently from 1940 to 1949. In the past decade, there has been a gradual supplanting of radiation therapy with hormonal regimes and surgical methods, either curettage alone or, if indicated, hysterectomy. In the last few years, sterilization for medical or psychiatric reasons has been done by irradiation only when surgery was contraindicated.

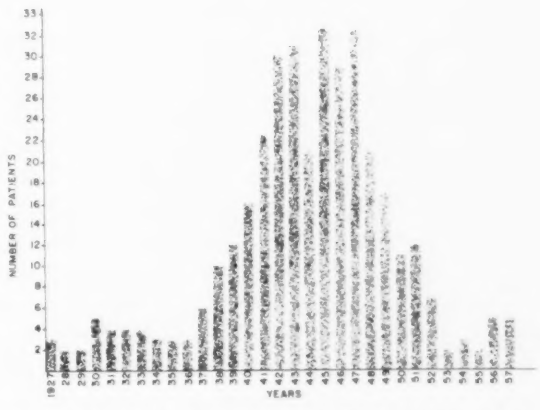


FIG. 1. Number of patients with benign gynecologic conditions treated each year.

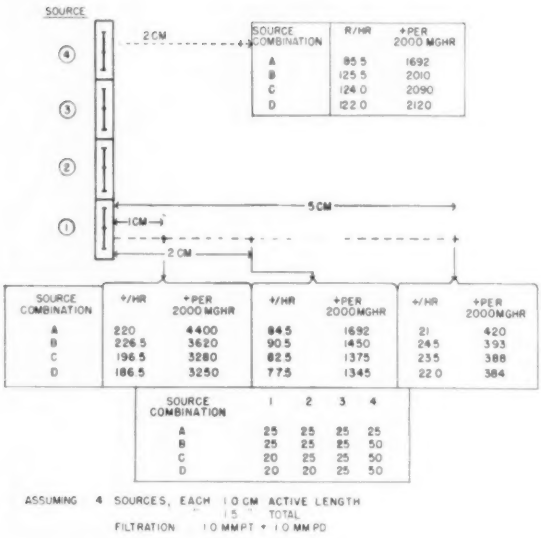


FIG. 2. Radium distribution and dosage in benign gynecologic lesions; assuming 4 sources, each of 1.0 cm. active length, and 1.5 cm. total length. Filtration: 1.0 mm. Pt and 1.0 mm. Pb.

Name:
Address:

1. Good response to x-ray or radium treatment was:
   Permanent_____
   Temporary_____
   None_____
2. Did menstrual bleeding recur? Yes_____
   No_____
3. If yes, was further x-ray therapy or surgery required?
   Yes_____
   No_____
4. If yes, name Hospital_____
   Physician_____
   Address_____
   Date_____
5. Present Health_____
6. Any other serious illnesses or operations?_____
   If yes, was hospitalization required?_____
   Name hospital, physician and date_____
7. Other remarks:

FIG. 3. Questionnaire sent to patients.

### AGE DISTRIBUTION

The main group of our patients was either menopausal or postmenopausal. The age bracket between forty and fifty-five years contained 82 per cent of our series. Only 14 per cent were below the age of forty and 4 per cent were past the fifty-five year mark.

### IRRADIATION TECHNIQUES

1. *Intrauterine Radium.* In 75 per cent of our cases, 359 patients, a radium stem was placed in the uterine canal. This consisted of a varying number of sources (1–5) filtered with 1.0 mm. Pt and 1.0 mm. Pb depending upon the length of the canal. The total amount of radium varied from 50 to 100 mg. and this was left in place from 24 to 50 hours. The average application was 2,400 mg. hr. ±400 mg. hr. The estimated dose in the pelvis to point A was 2,000 r (maximum) and to point B was 500 r (maximum). For a detailed analysis of treatment factors see Figure 2.

2. *External Irradiation.* A smaller group of 130 cases, or 25 per cent of our series, received external irradiation with the following factors: 220 kv., half value layer 1.0 mm. Cu, 2 opposing 15×15 cm. ports; the total dose to each port was 500–1,000 r, usually fractionally delivered in two weeks; the calculated midpelvic depth dose was 500–1,000 r (average 700 r).

### FOLLOW-UP METHOD

A regular form letter indicating our interest in evaluating the results of treatment was sent to all patients. The questionnaire consisted of seven carefully worded statements which were nonspecific in nature (Fig. 3). Of the 469 patients, 64 per cent responded, 25 per cent never received the letter and 11 per cent failed to return the questionnaire. Repeat questionnaires were sent to the latter two groups, personal investigations and telephone calls were made when feasible and letters to physicians, health department, etc. were mailed when indicated.

### CASES OF PELVIC MALIGNANCIES

The total number of cases of malignancy in our series following irradiation for benign uterine conditions came to 16 (Table III). Of these, 12 were pelvic and 4 were extrapelvic in location. Seven of the 12 were in gynecologic areas and the other 5 were in surrounding pelvic viscera. Brief case summaries (Table IV) of these pelvic malignancies are as follows.

CARCINOMA OF ENDOMETRIUM (3 CASES)

Case I. H.M., 165310, a forty-six year old female, was treated for menorrhagia with a 2,200 mg. hr. uterine stem radium application. Eight years later, a diagnosis of adenocarcinoma of the uterus was made which was treated preoperatively by Heyman's radium capsules followed by hysterectomy.

Case II. F.K., 69980, was a forty-three year old female with a history of menorrhagia shown to be due to endometrial hyperplasia following curettage. The application of a radium stem for 998 mg. hr. in 1942 was followed in 1949 by external roentgen irradiation calculated to deliver a depth dose of 720 r to the ovaries. Eight years later, recurrent menstrual bleeding was shown to be due to endometrial carcinoma which was treated preoperatively by Heyman's capsules followed by hysterectomy. Two and one half years later, she died of extensive metastases.

Case III. M.E., 13243, a forty-three year old female, was treated in 1935 for menorrhagia secondary to a myomatous uterus. A six point arrangement crossfiring the pelvis with roentgen irradiation was utilized with exposure factors recorded as 300 ma. min. Five years later a diagnosis of adenocarcinoma of the uterus was made. The patient followed a remarkable course, surviving for nineteen years with metastatic tumor the last ten years of life.

Table III

COMPARISON OF OBSERVED AND EXPECTED CANCER INCIDENCE IN THE PRESENT SERIES

| Site | Observed | Expected | Probability |
|---|---|---|---|
| Genital | | | |
| Corpus | 3 | 1.6 | 0.22 |
| Cervix | 1 | 1.8 | 0.83 |
| Ovary | 3 | 0.9 | 0.06 |
| Vagina | 0 | 0.05 | 1.00 |
| Vulva | 0 | 0.1 | 1.00 |
| Total Genital | 7 | 4.7 | 0.19 |
| Pelvic | | | |
| Bladder | 0 | 0.3 | 1.00 |
| Colon | 4 | 1.6 | 0.08 |
| Rectum | 0 | 0.6 | 1.00 |
| Anus | 1 | — | — |
| Total Pelvic | 5 | 2.5 | 0.11 |
| Total Genital and Pelvic | 12 | 7.2 | 0.06 |
| Breast | 4 | 4.4 | 0.64 |
| Total, All Sites (including 2 cases of cancer of the skin) | 18 | 17.6 | 0.49 |

CARCINOMA OF CERVIX (1 CASE)

Case IV. M.M., 195337, a forty year old patient, was treated for endometrial hyperplasia by means of a radium stem containing 115 mg. for 17 hr., totaling 2,000 mg. hr. Fifteen years later, carcinoma of the cervix was detected and death followed within a year's time.

CARCINOMA OF OVARY (3 CASES)

Case V. A.V., 144816, at the age of forty-nine had a bout of menorrhagia which led to the diagnosis of endometrial hyperplasia. Treatment was with insertion of 80 mg. of radium for 31 hr., or 2,480 mg. hr. Eight years later, at laparotomy, an extensive inoperable ovarian carcinoma was found and the patient died two months later.

Case VI. F.B., 132508, a fifty-two year old female with menorrhagia but normal endometrium, following curettage received 2,500 mg. hr. of radium (100 mg. for 25 hr.). She died shortly after the diagnosis of ovarian carcinoma at laparotomy eight years later.

Case VII. P.B., 145917, a forty-eight year old female presenting with menorrhagia but histologically normal endometrium, was treated by means of an 80 mg. radium tandem for 30 hr. (2,400 mg. hr.). A diagnosis of cystadenocarcinoma of the ovary was made thirteen years later. Therapy consisted of surgery, postoperative external irradiation and isotopic instillation. The patient is alive and well without disease for two years.

CARCINOMA OF COLON (5 CASES)

Case VIII. E.O'B., 58045, a fifty-five year old female with a history of menorrhagia, was treated by a radium application. She developed a sigmoid carcinoma two months later. Without much question this could not be related to the irradiation and is therefore excluded from our series.

Case IX. M.K., 206230, at the age of forty-five, developed a vesicovaginal fistula as the

TABLE IV

PELVIC MALIGNANCIES FOLLOWING IRRADIATION OF BENIGN LESIONS

| Case | Age | Indication for Treatment | Type of Treatment | Interval (yr.) | Late Cancer | Survival† (yr.) |
|---|---|---|---|---|---|---|
| I. H.M. 165310 | 46 | Menorrhagia | Radium | 8 | Endometrial | 1 |
| II. F.K. 69980 | 43 | Endometrial hyperplasia | Roentgen and radium | 8 | Endometrial | 2.5 |
| III. M.E. 13243 | 43 | Myomatous uterus | Roentgen | 5 | Endometrial | 19 |
| IV. M.M. 195337 | 40 | Endometrial hyperplasia | Radium | 15 | Cervical | 1 |
| V. A.V. 144816 | 49 | Endometrial hyperplasia | Radium | 8 | Ovarian | 8 |
| VI. F.B. 132508 | 52 | Menorrhagia | Radium | 8 | Ovarian | 1 |
| VII. P.B. 145917 | 48 | Menorrhagia | Radium | 13 | Ovarian | 2 |
| VIII. E.O'B. 58045* | 55 | Menorrhagia | Radium | 2 mo. | Sigmoid | 4 |
| IX. M.K. 206230 | 45 | Endometrial hyperplasia | Radium | 4 | Colon, ascending | 1 |
| X. R.G. 297450 | 50 | Endometrial hyperplasia | Roentgen | 5 | Sigmoid | 1 |
| XI. G.T. 345874 | 51 | Endometrial hyperplasia | Roentgen | 6 | Cecum | 2 |
| XII. M.S. 30679 | 42 | Endometrial hyperplasia | Roentgen | 12 | Sigmoid | 1 |
| XIII. M.J. 208479 | 50 | Endometrial hyperplasia | Radium | 11 | Anus | 5 |

* This case has been excluded from the series because the two month interval is too short for the carcinogenesis to be related to the irradiation.

† Still living.

result of repair of a cystocele. She also had menorrhagia and dilatation and curettage showed endometrial hyperplasia. She was treated with radium 70 mg. for 34 hr. totaling 2,380 mg. hr. Adenocarcinoma of the ascending colon was diagnosed four years after radium treatment and she died a year later of her disease.

CASE X. G.R., 297450, at the age of fifty developed menorrhagia and histologically proved endometrial hyperplasia. The following roentgen treatment factors were used: 220 kv., 15×15 cm. port anterior and posterior, and an ovarian dose of 480 r. The patient developed carcinoma of the sigmoid five years after irradiation. Resection of the sigmoid with ileocolostomy followed and she died shortly afterwards.

CASE XI. G.T., 345874, a fifty-one year old female, presented with vaginal bleeding due to endometrial hyperplasia with areas of atypia. Therapy was by means of external roentgen irradiation, 220 kv., half value layer 1.0 mm. Cu, 15×15 cm. anterior and posterior opposed pelvic fields. A depth dose of 1,714 r was delivered to the midpelvis. Six years later, a cecal carcinoma was found and resected. At death two years later, the disease had metastasized widely.

CASE XII. M.S., 30679, at the age of forty-two had metrorrhagia caused by histologically diagnosed endometrial hyperplasia. She was treated with 220 kv. roentgen rays with 15×15 cm. opposing ports, the anterior and posterior pelvis receiving a total dose of 684 r to each ovary. Twelve years later, at laparotomy, carcinoma of the sigmoid with metastases to ovaries and peritoneum was found.

### CARCINOMA OF ANUS (1 CASE)

CASE XIII. M.J., 208479, at the age of fifty developed metrorrhagia which was diagnosed histologically as endometrial hyperplasia. She was treated with radium 100 mg. for 24 hr., a total of 2,400 mg. hr. Eleven years later, she developed carcinoma of the anus which was treated by surgery and irradiation.

### COMMENT

Reviewing these cases of diverse tumors, one notes no correlation between their incidence and the age of the patient or the type of radiation employed. The ratio of radium applications to external roentgen treatments reflects the group distribution. The time interval before the onset of late cancer ranged from 4 to 15 years with the average being 8.7 years. It is of some inter-

est that the colon was the most frequent site of involvement.

### STATISTICAL METHODS AND RESULTS

The expected and observed incidence of cancer at various sites is given in Table III. The expected values are determined by the method devised by Corscaden *et al.*[1] in which the total person-years of exposure to risk at each age is calculated, and available tables of site and age-specific *incidence rates* are applied to calculate the expected number of cases at each of the sites. The incidence rates used are those released by the Bureau of Cancer Control of the State of New York, Department of Health, for the years 1949–1951, and, in addition, the table released for the year 1958. The table for 1958 is in abbreviated form and lists specifically only major sites. Wherever possible, the rates for 1949–1951 were averaged with those for 1958 to obtain the actual incidence rates used. For minor sites, *e.g.*, vulva, only the 1949–1951 rates were used. In no case did the rates differ much from those of the 1949–1951 table.

The use of any "control" or "normal" rate table is open to strong criticism. In the discussion it will be indicated that any group presented, as ours was, for treatment of benign gynecologic bleeding is, in fact, a special group. The only adequate control group would be a matched, similarly presented group which would *not* be treated by irradiation methods. It must be emphasized that we do not use the above indicated tables unreservedly. They are tables obtained from *reported* cases (cancer has been reportable by law in New York State since 1940), including those reported on death certificates. They are for all of New York State, exclusive of New York City. They are based, at least partially, on population estimates. The same tables were used by Palmer and Spratt[15] and by Stander.[19]

A third column is included in Table III in which we have calculated the probability of at least as many incidents as were observed by us with the indicated expected values. It is notable that, although the number of cases is high for the ovary and for the colon, the over-all number of genital cases is not exceptionally high—nor is the over-all number of pelvic cancers. Compounded still further, however, the total number of pelvic region cases (12) is probably high and has a probability of only about 1 in 20 of occurring in groups of this size.

It should also be noted that the total incidence observed for cancer of all sites (including skin cancer) is 18, whereas the expected number using control rates is 17.6 —almost identical!

It is our feeling that these probability figures are useful in deciding whether or not there is really an increased incidence at a particular site or combination of sites. The calculation of an observed-expected ratio is grossly misleading and inaccurate. It is misleading because it *assumes* that there is a real increase in incidence. It is inaccurate because it fails to take into account chance deviations. Considerably smaller rate increases than those expressed by the ratio could account for the observed incidence.

If we accept the control rates as valid, the probability number tells how likely we are to get as many (or more) cases as observed in a sample made up of a similar number of person-years. Roughly speaking, a probability of 0.16 indicates a difference of about 1.0 standard error and a probability of 0.05 corresponds to a difference between observed and expected of about 1.7 standard error. For mass survey samplings and biologic experimentation, a difference of 1.0 standard error is not significant, whereas 2.0 standard errors or more are statistically significant.

### DISCUSSION

The incidence of pelvic malignancy following irradiation for benign gynecologic conditions varies from series to series. The elusiveness of conclusions is due to the pitfalls inherent in mass surveys of this sort. First, a suitable control group is not available. The use of expected incidence

rates in a general population such as that of Upstate New York is a compromise in that the group of patients under scrutiny has been selected because of a gynecologic disorder. The ideal control group would be one in which a group of women with benign gynecologic lesions, uncomplicated by therapy for endometrial hyperplasia, was followed up to establish the rate of pelvic malignancy, Secondly, the limitations of any data are length and completeness of follow-up, both of which are less than ideal. Thirdly, menopausal menstrual disturbances may be predisposing factors for the subsequent development of malignancy as well as the indication for irradiation.

In evaluating the data of the statistical analysis, the two critical aspects of the problem to be emphasized are the role of predisposing diseases and the role of irradiation in regard to the incidence of genital cancers. In addition, an evaluation of other pelvic and extrapelvic malignancies will be presented.

### THE ROLE OF PREDISPOSING DISEASE

1. *Significance of Endometrial Hyperplasia.* The significance of this disorder in causing cancer must be carefully weighed. Randall[16] found that women with a history of menorrhagia during climacteric have a three and one-half times greater chance of developing uterine fundal cancer than do the women who experience no increased bleeding prior to cessation of their menses. Corscaden *et al.*[1] and Stander[19] noted that the number of cases of endometrial cancer in their studies exceeded the expected number by a factor of 3 to 4 and concluded, as did Randall,[16] that this reflected a predisposition of these patients to develop cancer and that radiation *per se* is not an etiologic factor. Novak and Yui[13] referred to the endometrial hyperplasia as a process possibly preceding malignant change in the endometrium. Hertig and Sommers[6] concluded that cystic hyperplasia rather than adenomatous hyperplasia was an important precursor to cancer, though both were predisposing conditions. In another series,[19] generalized hyperplasia was more predominant than cystic or interstitial hyperplasia in accounting for the majority of cancer cases.

2. *Significance of Fibroid Uteri.* Fibroid uteri were the next largest group in our series. The incidence of adenocarcinoma in myomata uteri is the same as that for nonmyomatous uteri according to Randall.[16] This has been confirmed by other authors, and ranges from 1 per cent to 2 per cent. Only 1 patient in our entire series who was irradiated for myomata later developed an endometrial lesion, for a 1.0 per cent occurrence rate.

3. *Excessive Estrogen Secretion.* Excessive estrogen stimulation in menopausal irregularities is well known and underlying ovarian pathology may be present. Estrogen secreting tumors are frequently associated with adenocarcinoma of the uterus. The incidence of ovarian carcinoma may, in part, be accounted for on this basis since it is a more difficult area to examine adequately from a histologic viewpoint than the endometrium or cervix, which are readily available for biopsy.

4. *Endocrine Imbalance.* Estrogen withdrawal induced by radiation menopause may upset the anterior pituitary feed-back mechanism and lead to periods of prolonged pituitary stimulation of the endometrium and ovaries. This may in turn result in successive morphologic changes ending in cancer, according to Hertig and Sommers.[5,7]

### THE ROLE OF IRRADIATION

1. *Animal Experimentation.* In alluding to Furth's[4] concept of neoplasia as an unrestrained growth, it is worth emphasizing that irradiation may not only be a mutating factor in direct permanent alteration of cells but may also act indirectly on extracytogenic forces which may lead to derangement of the balance between endocrine organs. There is evidence to suggest that this latter factor may be more important in ovarian tumorogenesis.

Irradiation of the pelvis in an attempt to induce carcinomas has been undertaken in

mice and rats. Furth[4] has stated that three basic factors are operating in ovarian tumorogenesis: (1) increase in gonadotrophes due to ovarian atrophy, (2) failure of irradiated ovarian cells to regulate the activity of gonadotrophes, and (3) disorganization of this organ initiated by injury of the ova. It is the disappearance of the ova which hastens senescence; when this occurs the hormonal status is altered and this, in turn, creates a sensitive state for tumor development. Administration of estrogens or protection of one ovary reduces the incidence of ovarian tumors. Uterine tumors have been induced by gamma rays in rabbits by Lorenz but their pathogenesis has not been determined.

2. *Low Dose versus High Dose Irradiation.* The meaning of low dose and high dose irradiation in regard to carcinogenesis has received some attention in the literature. The finding that the development of cancer was greater in the low dose irradiation group has suggested to the Roswell Park Memorial Hospital investigators a growth stimulating factor of roentgen rays. This is probably not entirely accurate but has some validity in that reaction to radiation injury leads to hyperplasia and then to neoplasia, which may not occur after high doses; *i.e.*, a large dose of radiation may eliminate the regenerative capacity of tissues completely. Ovarian tumors seem to have a threshold level (600 r) which is at the point of cessation of function.[4]

3. *The Time Lag.* The time lag of five to twenty years has been mentioned by Palmer and Spratt[15] as a factor favoring radiation as the inciting cause of carcinogenesis. Unfortunately, there are few studies of the endometrium prior to the development of adenocarcinoma in uncomplicated cases. Hertig and Sommers[6] report that the highest incidence of cystic hyperplasia was found up to thirteen years before the development of carcinoma, whereas adenomatous hyperplasia was noted one to thirteen years before the diagnosis of carcinoma. This compares reasonably well with the average time interval of eight years after irradiation and in and of itself constitutes no evidence in support of the theory that radiation rather than the underlying pathology is the cause of the carcinogenesis.

4. *Protective Effects.* It is again worth mentioning that the only sizeable series in which there was an attempt to present a control group was that of Crossen and Crossen.[3] The fact that the incidence of both ovarian and endometrial cancer was significantly lowered in irradiated, as opposed to nonirradiated, patients cannot be lightly dismissed. Rather, it emphasizes the need for similar controlled studies which, unfortunately, are most difficult if not impossible to obtain.

### GYNECOLOGIC VERSUS OTHER PELVIC VISCERAL CANCERS

The gynecologic cancers have been adequately analyzed as to cervical, endometrial and ovarian neoplasms. Vaginal and vulvar lesions were absent in our series. The unusually high incidence of vaginal carcinoma found by the Roswell Park Memorial Hospital group[15] may be due to the low expected incidence figure or to the inclusion of metastatic lesions as primary cancers. This is seen in both their high and low dose category and is the only series of cases that shows this pattern.

An unexpected finding in our series was the 4 cases of colon carcinoma (excluding the 1 case which developed two months after irradiation). Three of these cases were in the sigmoid colon and 1 in the cecum; both segments are close to if not in the pelvis. No bladder carcinoma was found. The other series of lower bowel carcinomas are those of Corscaden *et al.*,[1] Stander[19] and Palmer and Spratt.[15] Stander[19] did not feel that the observed number exceeded the anticipated number by any significant degree. It is of particular interest that Palmer and Spratt's report[15] listed 7 rectal but no colon cancers. Since virtually every other category of pelvic neoplasia was high, this absence of a single case of colon neoplasm points up the difficulty in draw-

TABLE V

SUMMARIZED COMPARISON OF RESULTS OF LATE CARCINOGENESIS FOLLOWING PELVIC IRRADIATION

| | Genital | | | | | Other Pelvic Sites | | | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Corpus | Cervix | Ovary | Vagina | Vulva | Bladder | Colon | Rectum | Anus | No. | Per Cent |
| Schmitz[18] | 1 | 0 | 0 | 0 | 0 | — | — | — | — | 1 | 0.17 |
| Costolow[2] | 3 | 1 | 0 | 0 | 0 | — | — | — | — | 4 | 0.40 |
| Corscaden *et al.*[1] | 9 | 6 | 2 | 0 | 0 | 2 | 2 | 2 | 0 | 23 | 2.50 |
| Crossen and Crossen[3] | 4 | 0 | 1 | 0 | 0 | — | — | — | — | 5 | 0.95 |
| Montgomery *et al.*[12] | 9 | 2 | 1 | 0 | 0 | — | — | — | — | 12 | 1.40 |
| Hunter *et al.*[8] | 2 | 0 | 1 | 0 | 0 | — | — | — | — | 3 | 0.50 |
| Palmer and Spratt[15] | 29 | 11 | 8 | 2 | 1 | 3 | 0 | 7 | 0 | 61 | 8.40 |
| Stander[19] | 14 | 0 | 4 | 0 | 1 | 0 | 4 | 3 | 0 | 26 | 3.70 |
| Rubin *et al.* | 3 | 1 | 3 | 0 | 0 | 0 | 4 | 0 | 1 | 12 | 3.90 |
| Total | 74 | 21 | 20 | 2 | 2 | 5 | 10 | 12 | 1 | 147 | |

ing dogmatic conclusions about the susceptibility of a specific anatomic site.

### EXTRAPELVIC TUMORS

Extrapelvic lesions such as those of the lung and larynx represent isolated instances. Breast carcinoma was below the anticipated rate in the present series as well as in that of Palmer and Spratt[15] who concluded that this showed that their series was not studied with prejudice and was not cancer prone. In Stander's study,[19] the expected number, except for breast cancer, was not encountered. There could be an argument for radiation menopause as a prophylactic measure against the development of breast carcinoma; however, this concept is neither credited nor discredited at the present stage of our clinical knowledge.

Apart from the more recent studies, no mention is made of extrapelvic tumors. The finding of 1 or 2 cases in different categories, where only a fraction of a case was expected, demonstrates one of the weaknesses of utilizing an expected-to-observed ratio rather than a probability factor. Since patients do not enter as fractions, the finding of a single case may be four to ten times the control value which forms the denominator in the ratio.

### CONCLUSIONS

In concluding this survey, two questions arise:

(1) *Has irradiation of benign gynecologic malignancies resulted in the induction of pelvic malignancies?* All of the more carefully documented series are presented in a summary form in Table v. Considering the total number of pelvic malignancies, the percentage incidence varied from 0.17 per cent to 8.4 per cent. This includes not only genital cancers but bladder, colon, rectal, and anal cancers as well. The last three series are highest in incidence and this may reflect the longer average follow-up, which exceeded ten years. If Palmer and Spratt,* with the lowest response rate to their questionnaires (43 per cent), would include their whole series in the calculation, their percentage incidence would be 3.6 per cent, which is more consistent with the other two studies.

The largest single group of late tumorogenesis was endometrial carcinoma followed by ovarian and cervical carcinomas. The latter lesions, except in Palmer and Spratt's group, occurred as sporadically as vaginal and vulvar neoplasia. The opinion of most authors is that the predisposing condition rather than radiation *per se* is the etiologic factor in the gynecologic neoplasms noted. From the figures in our series, the same conclusion seems warranted.

* In a personal communication, Dr. Spratt agreed with the validity of such re-evaluation of his report.

In contrasting the tabulated figures of Palmer and Spratt[15] (Table VI) to those of Stander[19] (Table VII), which have been re-evaluated as probability figures, the two horns of the dilemma are revealed. The two studies are quite comparable in that a similar number of patients (about 700) were followed for an average of seventeen years, for approximately 12,500 patient years. The expectancy values were derived from the same source. In the Ann Arbor presentation, the probability for genital, pelvic, and combined genital and pelvic cancers is not considered highly significant. The Roswell Park Memorial Hospital experience is highly significant in virtually every category, with each showing an increased finding of cancer. The present series from Strong Memorial Hospital (Table III) falls between these two reports in significance but is more comparable to the Stander results. The need for documentation of more experiences is readily apparent.

(2) *Should radiation therapy be abandoned in treating benign conditions?* In regard to benign gynecologic conditions, one must weigh the success as well as the morbidity and mortality of surgical procedures against that of radiation therapy. It must be appreciated that the mortality from anesthesia and surgery is as high as that of late carcinogenesis. Montgomery *et al.*[12] in analyzing their experience felt that the risks with radium were less than those with surgery. The complications of benign conditions, though not lethal, can be debilitating and distressing and are difficult to weigh against the morbidity associated with treatment. This is particularly true when the complication percentage figures are so small. Few procedures are without risk in medicine but it is essential to establish these risks.

As surgery, anesthesia, and pharmaceuticals improve, radiation therapy will be used less and less for benign lesions. It should not be the fears but rather the facts which direct treatment plans. At present, the uncertainties raised by the question of late carcinogenesis have led, in part, to con-

TABLE VI

LATE CANCER INCIDENCE IN THE PALMER AND SPRATT SERIES[15]

| Site | Observed | | Expected | | Probability |
|---|---|---|---|---|---|
| Genital | | | | | |
| Corpus | 29 | | 4.86 | | 0.001 |
| Cervix | 11 | | 6.53 | | 0.040 |
| Ovary | 8 | | 2.58 | | 0.005 |
| Vagina | 2 | | 0.17 | | 0.020 |
| Vulva | 1 | | 0.33 | | 0.300 |
| Total Genital | | 51 | | 14.47 | <0.0001 |
| Pelvic | | | | | |
| Bladder | 3 | | 0.82 | | 0.05 |
| Colon | 0 | | 3.70 | | |
| Rectum | 7 | | 2.11 | | 0.01 |
| Total Pelvic | | 10 | | 6.63 | 0.24 |
| Total Genital and Pelvic | | 61 | | 21.10 | <0.0001 |
| Breast | 10 | | 14.30 | | 0.91 |

*Conclusion:* Highly significant

TABLE VII

LATE CANCER INCIDENCE IN THE STANDER SERIES[19]

| Site | Observed | | Expected | | Probability |
|---|---|---|---|---|---|
| Genital | | | | | |
| Corpus | 14.0 | | 4.3 | | 0.001 |
| Cervix | 0.0 | | 6.7 | | 1.00 |
| Ovary | 4.0 | | 3.1 | | 0.38 |
| Vagina | 0.0 | | 0.2 | | 1.00 |
| Vulva | 1.0 | | 0.4 | | 0.33 |
| Total Genital | | 19.0 | | 14.7 | 0.16 |
| Pelvic | | | | | |
| Bladder | 0.0 | | 0.8 | | 1.00 |
| Colon | 4.0 | | 3.7 | | 0.51 |
| Rectum | 3.0 | | 2.2 | | 0.38 |
| Total Pelvic | | 7.0 | | 6.7 | 0.51 |
| Total Genital and Pelvic | | 26.0 | | 21.4 | 0.20 |
| Breast | 9.0 | | 13.6 | | 0.91 |

*Conclusion:* Not highly significant

servative policies with more rigid criteria for radiation therapy in benign gynecologic lesions. The final decision in each case must be made by the referring physician and the radiotherapist. The answer will depend on their experience and philosophy, since no consistent conclusion is available in the literature.

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# THE TREATMENT OF ANAL CARCINOMA BY INTERSTITIAL IRRADIATION*

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CANCER of the anus is an uncommon lesion and the problems associated with its management are somewhat overshadowed by those of rectal cancer. Treatment by interstitial irradiation has been widely practiced and at the present time, when supervoltage equipment is increasingly available, it is interesting to consider the results of treatment by this method.

## CLINICAL MATERIAL

*Cases Studied.* At the Christie Hospital & Holt Radium Institute, from 1932 to 1955, 171 new cases were seen. This represents 0.2 per cent of all previously untreated malignant cases registered, and a rate per million of 1.8. The latter figure is low, as it is arrived at by consideration only of the number of patients referred to this hospital (in a region with a population of four and one-half million), and therefore takes no account of possible cases referred to other hospitals in the area. Roux-Berger and Ennuyer[6] reporting from the Fondation Curie stated that, out of 10,000 patients, 0.58 per cent had true anal lesions.

Of the 171 cases comprising the present study group, 34 were considered to be so advanced that no useful treatment was possible; 31 cases were referred for surgery; and 106 cases were treated by irradiation. It is this latter group with which this paper is mainly concerned (Table I).

*Sex Incidence.* McQuarrie and Buie[4] and Murphy[5] found a higher incidence of the disease in females; on the other hand, Sweet's[7] series of 77 cases contained more males, and Gabriel[2] reported an equal sex distribution. In this series, there are 102 males and 69 females—a ratio of almost 4:3.

TABLE I

CANCER OF THE ANUS
1932–1955

| | |
|---|---|
| Number of Cases Reviewed | 171 |
| Cases Referred for Surgery | 31 |
| Cases Too Advanced for Treatment | 34 |
| Cases Treated by Irradiation | 106 |

*Age.* The average age at the date of first examination was 64 years, which concurs with other published figures, *viz.*, Gabriel,[2] 61.7 years and Williams,[8] 62 years.

*Histology.* Cancer of the anus arises both in the modified squamous epithelium of the anal margin and lower anal canal below the pectinate line, and in the cuboidal epithelium lining the canal between the pectinate line and the anorectal ring. (This latter tissue may indeed also be modified squamous epithelium, as suggested by Goligher, Leacock and Brossy.[3]) The distribution of histologic types in the 106 cases treated by irradiation is shown in Table II.

*Site.* It is usual to consider cancer of the anus as arising in either the anal canal proper or at the anal margin; in this largely

TABLE II

FREQUENCY DISTRIBUTION BY HISTOLOGIC TYPE

| Histology | No. of Cases |
|---|---|
| Carcinoma—Squamous Cell | 90 |
| Carcinoma—Transitional Cell | 6 |
| Carcinoma—Basal Cell | 1 |
| Carcinoma—Basi-squamous Cell | 1 |
| Not Apparent | 2 |
| No Section Taken | 6 |
| Total | 106 |

* From the Christie Hospital & Holt Radium Institute, Manchester, England.

TABLE III

FREQUENCY DISTRIBUTION BY SITE AND SEX

| Site | No. of Cases | Male | Female |
|---|---|---|---|
| Anal Margin | 41 | 28 | 13 |
| Anal Margin and Canal | 48 | 38 | 10 |
| Anal Canal | 33 | 16 | 17 |
| Anal Canal and Rectum | 49 | 20 | 29 |

TABLE IV

CLINICAL STAGING OF 98 HISTOLOGICALLY PROVED TREATED CASES

| Site | Clinical Stage | | |
|---|---|---|---|
| | Early | Moderately Advanced | Advanced |
| Anal Margin | 17 | 9 | 4 |
| Anal Margin and Canal | 9 | 13 | 10 |
| Anal Canal | 7 | 3 | 10 |
| Anal Canal and Rectum | — | — | 16 |
| Total | 33 | 25 | 40 |

retrospective study, however, it has not been possible to be so exact and the cases have been placed in four groups (Table III). This division has proved to be of some prognostic value, as will be seen later. It also confirms the belief that cancer of the anal margin is more common than cancer of the anal canal in males; the difference is, however, by no means as striking as in other reported series, such as that of Gabriel.[2]

*Stage of Disease.* There is no generally accepted method of clinical staging in cancer of the anus. In this series, cases have been classified as early, moderately advanced or advanced, according to the site of the lesion and the local metastatic spread (Table IV).

An interesting fact which emerged here is that the females presented at a later stage than the males. Of the 98 histologically proved treated cases, 54.5 per cent of the female group were classified as advanced compared to only 33.8 per cent of the males. This is due—in part at least—to the prevalence of cancer of the anal margin in males; it is a visible and easily palpable lesion which is likely to be noticed by the patient at a relatively early stage.

## TREATMENT

*The Primary Lesion.* There is no general agreement on the treatment for cancer of the anus; some authorities advocate surgery, others radiation therapy. Surgery, though of potentially high curative value, necessitates in most cases a permanent colostomy, which is distressing to the majority of patients. Successful irradiation results in normal function and is, therefore, preferable whenever possible as the first treatment in cases of limited size, with surgery reserved for possible future use.

Squamous cell carcinoma of the anus of small or moderate size is curable by irradiation; it is, however, a tumor of limited radiosensitivity and this fact, added to the knowledge that the tissues of the perineal region are notoriously intolerant to high dose irradiation, means that great care must be taken in planning treatment. External irradiation to radical dosage results in a reaction which is extremely painful and, if taken to curative levels, carries a high risk of tissue necrosis. Williams[8] reported 23 cases of carcinoma of the anal canal treated by supervoltage roentgen therapy of which 5 developed serious radiation necrosis.

We consider that, as will be shown later, the results of interstitial irradiation justify this as the method of choice for limited anal lesions. In the case of extensive lesions —and these include most of our 49 cases classified as anal canal and rectum carcinomas—radiation therapy will almost certainly fail and will seldom produce worthwhile palliation; an increasing awareness of this has resulted in fewer such cases being treated in this hospital in recent years.

The majority of the interstitial treatments consisted of single plane and two plane implants; occasionally, particularly in the earlier years, volume implants were

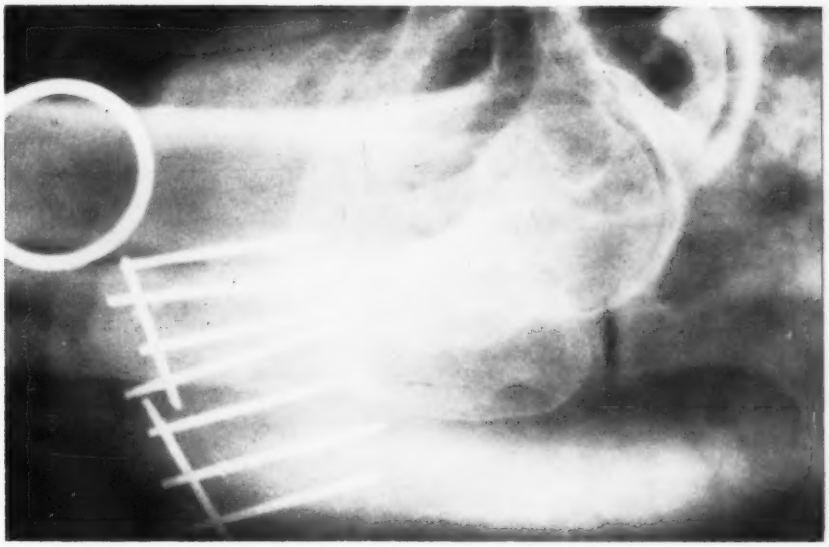

Fig. 1. Single plane radium needle implant, lateral view.

performed for rather large lesions and were sometimes combined with intracavitary radium. Most of these latter cases did badly and the method has fallen into disuse, though not, perhaps surprisingly, because of a high incidence of necrosis, but rather because of its inability to cover adequately the whole tumor area.

For small unilateral lesions a single plane implant is employed, aiming at a dose of 6,000 $r_\gamma$ in seven days (Fig. 1). For thicker lesions, or those involving both sides of the anus, a two plane implant is necessary; the dose should not be more than 5,500 $r_\gamma$ in seven days (Fig. 2, *A* and *B*).

*Lymph Node Metastases.* The lymphatic drainage of the anal margin and canal is predominantly to the superficial inguinal lymph nodes, though some of the upper lymphatics of the canal drain directly to the anorectal or hypogastric lymph nodes.[1] Of the 98 histologically proved cases in this series, 24.5 per cent had clinically significant lymph node involvement in the inguinal region within three months of the first examination and the incidence by site is shown in Table v. In 2 cases, both groins were involved.

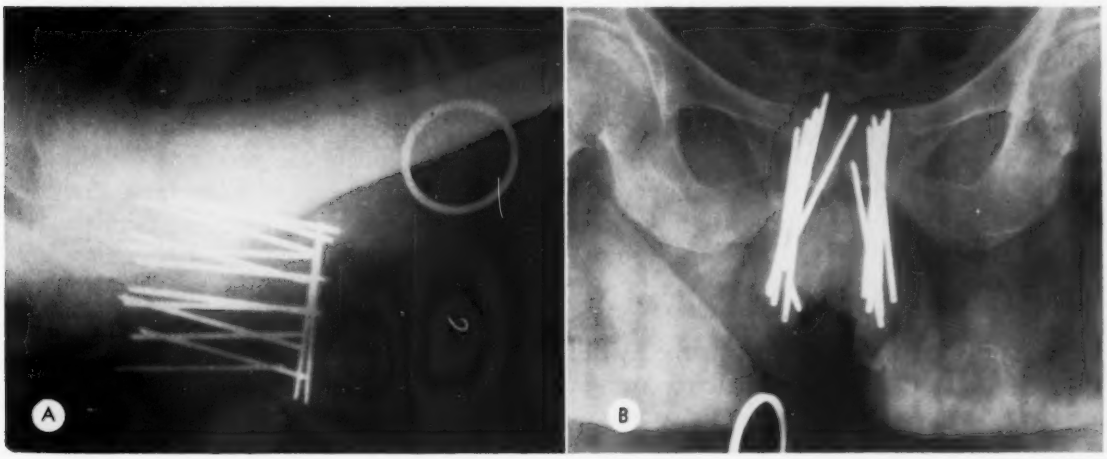


Fig. 2. Two plane radium needle implant. (*A*) Lateral view and (*B*) anteroposterior view.

TABLE V

LYMPH NODE INVOLVEMENT IN 98 CASES WITHIN THREE MONTHS OF FIRST EXAMINATION

| Site | No. of Cases | Cases with Lymph Node Involvement | |
|---|---|---|---|
| | | Number | Per Cent |
| Anal Margin | 30 | 3 | 10.0 |
| Anal Margin and Canal | 32 | 11 | 34.4 |
| Anal Canal | 20 | 3 | 15.0 |
| Anal Canal and Rectum | 16 | 7 | 43.8 |

Mobile involved inguinal lymph nodes are best treated by block dissection of the groin. The results of irradiation are so poor that this method should never be preferred to surgery in potentially curable cases; it is indeed very doubtful if the treatment of even inoperable lymph node involvement by irradiation achieves any palliation in a sufficient number of cases to justify its use.

## MANAGEMENT

The management of the patient prior to, during and after implantation of radium is very important and we have thought it worthwhile to describe the routine care of a case as undertaken at this hospital. Admittance is arranged three days before the implantation is to be done. The patient is given a very light diet and an aperient is administered on the first evening, followed by enemas on the second and third days, with a final bowel washout the afternoon of the third day. The night before operation, the patient is given 30 min. tinct. opii and on the morning of operation this is repeated; during the first six days of a seven day implant, 20 min. tinct. opii is administered twice a day. With this regime it is nearly always possible to keep the patient constipated throughout the time the radium needles are in position. On the seventh day and the day following removal of the radium needles, the patient is given petrol agar twice daily. This usually results in a resumption of normal bowel habit—if not, a glycerine suppository is given.

The patient is nursed on the side with a thin pillow between the knees and anal swabbing with a bland solution such as sodium bicarbonate is carried out up to three times daily; an antibiotic is not routinely given. After removal of the radium needles, the patient is given a bath twice daily, with swabbing of the perineum after each bowel action. The length of time spent in the hospital is three to five weeks depending on the size of the implant and the severity of the reaction. It is essential to instruct the patient in the importance of regular bowel movement—so often there is a tendency to constipation because of the discomfort following treatment, and petrol agar is often necessary for some time. If control of defecation is good prior to treatment, there is usually no reason to expect deterioration afterwards.

## COMPLICATIONS

Local tissue necrosis is the complication to be feared after irradiation of anal cancer. Of 98 histologically proved treated cases available for three year follow-up, 23 (or 23.4 per cent) developed such a necrosis. Of these, only 10 were of a serious nature, 6 requiring colostomy and 4 excision. The remainder healed satisfactorily after a period of nursing sometimes combined with light diathermy. Anal stricture of a marked degree occurred in only 1 case.

## RESULTS

Of the 106 cases treated by irradiation, 6 were regarded as incurable from the beginning and received only palliative treatment; these cases have been excluded from the series when assessing results. Also excluded are 8 cases not histologically proved. For analysis there are 92 cases and the survival at three, five and ten years is shown in Table VI.

In a series containing a high proportion of old people, which is the case in cancer of the anus, some form of corrected rate is desirable, since deaths from causes other

TABLE VI

SURVIVAL RESULTS OF RADICAL TREATMENT

| Interval (yr.) | No. of Cases | Survival | | |
|---|---|---|---|---|
| | | No. of Survivals | Crude Rate (per cent) | Age Corrected Rate (per cent) |
| 3 | 92 | 46 | 50.0 | 55.2 |
| 5 | 85 | 37 | 43.5 | 51.2 |
| 10 | 61 | 17 | 27.9 | 50.7 |

than cancer of the treated site occur at an accelerated rate as the after-treatment interval lengthens.

The age corrected method of calculation first suggested by Berkson in 1942, approved by the World Health Organization Sub-Committee on Registration of Cancer in 1950 and discussed and applied in the Third Statistical Report from the Christie Hospital & Holt Radium Institute in 1950 has been used to correct for the number of deaths that would be expected to occur under prevailing conditions of mortality in a population having the same sex and age distribution as the treated series. This rate may be expressed as:

$$S.R._{cor.} = \frac{\text{Number alive and treated after } n \text{ years}}{\text{Expected number of survivors after } n \text{ years}}$$

The results analyzed by site and stage are shown in Tables VII and VIII. Cancer of the anal margin has the best prognosis; metastatic spread to lymph nodes is uncommon and the highest percentage of early cases was found in this group. However, with such small numbers of cases, the difference in percentage survival is not statistically significant. Study of those cases either presenting with clinically evident involvement of inguinal lymph nodes or developing it within three months reveals that all but 2 of the cases are dead: 8 further cases developed metastatic lymph nodes later, and none survived. It is evident that the prognosis of cases with regional lymph node deposits is extremely poor.

Surgery for residual or recurrent cancer was undertaken in 21 of the 92 radically treated cases, and 13 of the 21 are alive and well three years later.

TABLE VII

FIVE YEAR SURVIVAL RESULTS ANALYZED BY SITE

| Site | No. of Cases | Survival | |
|---|---|---|---|
| | | No. of Survivals | Age Corrected Rate (per cent) |
| Anal Margin | 26 | 14 | 63.4 |
| Anal Margin and Canal | 31 | 14 | 53.2 |
| Anal Canal | 15 | 6 | 47.1 |
| Anal Canal and Rectum | 13 | 3 | 27.2 |

TABLE VIII

FIVE YEAR SURVIVAL RESULTS ANALYZED BY STAGE

| Clinical Stage | No. of Cases | Survival | |
|---|---|---|---|
| | | No. of Survivals | Age Corrected Rate (per cent) |
| Early | 31 | 19 | 72.2 |
| Moderately Advanced | 20 | 11 | 64.8 |
| Late | 34 | 7 | 24.3 |

## CONCLUSION

Treatment of cancer of the anus by interstitial irradiation, with surgery in reserve, has yielded a five year corrected survival rate of 51.2 per cent. This has been achieved in the majority of cases with the preservation of normal function, and with careful planning the complications have not been severe. For early and moderately advanced lesions, radium implantation provides a satisfactory method of treatment.

## SUMMARY

There were 171 cases of cancer of the anus seen at the Christie Hospital & Holt Radium Institute from 1932 to 1955 and these are reviewed. Treatment by interstitial irradiation, with surgery in reserve, has

been employed in the majority of cases and the results of this treatment are presented.

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Vol. 85, No. 3

# LYMPHOSARCOMA: SURVIVAL AND THE EFFECTS OF THERAPY*

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THE therapeutic regimen of choice for patients with lymphosarcoma is predominantly that of radiation therapy. This has been true for many years and has remained so despite the initial impression that alkylating agents, anti-metabolic drugs and adrenal steroids might be more valuable in the control of the disease.[1,3,4,6,14,21,30] In order to arrive at such a conclusion, it has been of benefit to objectively review the therapeutic results over a period of years at one institution.

Over a thirty year period numerous patients with lymphosarcoma have been treated at the Memorial Center for Cancer and Allied Diseases. Histologic criteria for diagnosis have been strict and constant.[3,6,8,26,30] The experience has been that of one institution, largely under the direction of one physician (L.F.C.), and has recently been critically reviewed.[27]

This report presents the information derived from this analysis as it pertains to the effects of therapy and survival. Data describing the histologic classification, transitions of the disease, and age and sex distribution of the group will also be presented.

## MATERIAL

*Case selection.* All hospital and outpatient records from 1928 to January 1, 1958 bearing the diagnoses of lymphosarcoma, reticulum cell sarcoma or giant follicular lymphosarcoma were carefully studied. To allow at least a five year period of follow-up, only those patients whose clinical onset of disease occurred prior to January 1, 1953 were included in this analysis. A total of 1,635 charts were reviewed. Of these, 366 were excluded, usually because of the lack of conclusive tissue examination at this institution or because of obvious lymphatic leukemia at the first visit.

TABLE I

HISTOLOGIC TYPES OF LYMPHOSARCOMA (1,269 CASES)

| | |
|---|---|
| Giant Follicular Lymphosarcoma | 162 |
| Lymphosarcoma | 553 |
| Reticulum Cell Sarcoma | 554 |
| Total | 1,269 |

The remaining 1,269 cases comprise the study group, material from which will be presented in this report. This group includes not only cases designated and filed as generalized lymphosarcoma, but also those cases which could be located under lymphosarcoma filed under such regional classifications as malignant lesions of the tonsil, stomach, bone, skin, mediastinum, etc.

## HISTOLOGIC CLASSIFICATION

The histologic classification of these tumors is not uniform, not only from institution to institution, but also from pathologist to pathologist within one institution and probably also for the same pathologist over a period of years.[10–12,16,21,25,32,33] Therefore, we have chosen to utilize the general subdivisions shown in Table 1.[3,8,26,30] These diagnoses were either rendered by a senior member of the Pathology Department of Memorial Center or were accepted after review by Drs. John Berg and Stephen Sternberg.

* From the Lymphoma Service, Department of Medicine, Memorial Center for Cancer and Allied Diseases; the Lymphoma Section of the Division of Clinical Chemotherapy, Sloan-Kettering Institute for Cancer Research; and the Department of Medicine, Cornell University Medical College, New York, New York.
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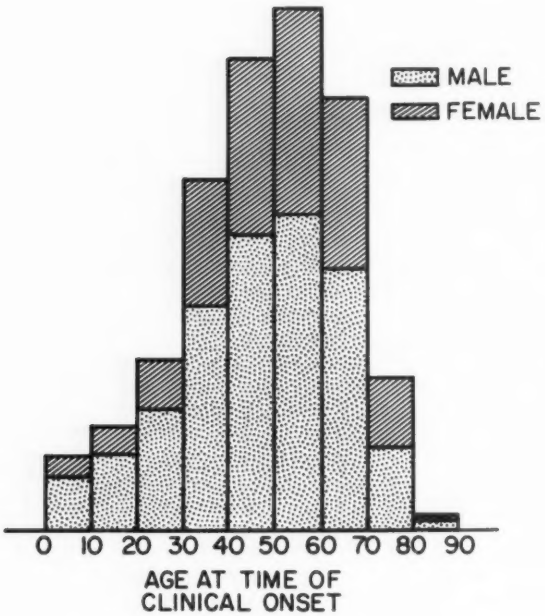


FIG. 1. Age and sex distribution of 1,269 cases of lymphosarcoma.

AGE AND SEX DISTRIBUTION

The diseases are more frequent in males than in females in all age groups, the average ratio being 1.7 to 1.0. Figure 1 shows the age and sex distribution of the entire group. The age range, at the time of the clinical onset of the disease, extends from 22 months to 92 years. The greatest number of cases is seen during the fifth decade of life and the median age for the entire group is 49.7 years. Figure 2 shows the relative incidence of disease, relating the number of cases to the United States population figures for the approximate midpoint of the study and demonstrating the increasing relative incidence with age, except for the oldest age group.

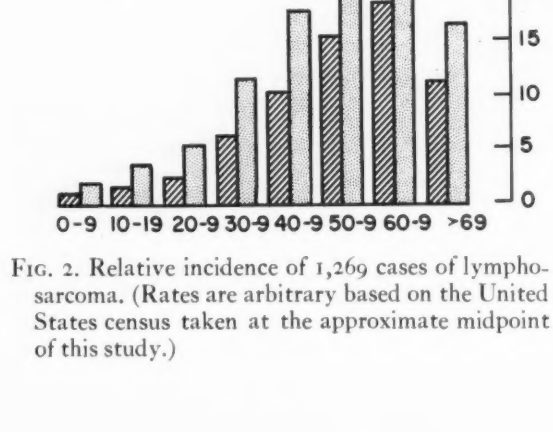


FIG. 2. Relative incidence of 1,269 cases of lymphosarcoma. (Rates are arbitrary based on the United States census taken at the approximate midpoint of this study.)

TRANSITIONS TO LEUKEMIA

There is much confusion and disagreement concerning the interrelationships between these tumors of lymphoid origin and lymphatic leukemia.[2,6,17,28,32,33] Such terms as leukosarcoma, leuko-lymphosarcoma, lympho-leukosarcoma and reticulum cell leukemia have been proposed for the frequent, apparent leukemic transformations occurring in this group of diseases. These terms are meaningful chiefly to those who have defined them and there is little uniformity of usage. The therapeutic implications, however, of the generalization of the disease as manifested by a leukemic change make it necessary for the physician to recognize such a transformation. It is the recognition that this transition can occur which is important, rather than the name applied to it.

As indicated by Table II, 7.6 per cent of the total group demonstrated leukemic changes. This occurred more often in children than in adults. The change was seen less often in reticulum cell sarcoma than in the other histologic categories. Acute blastic leukemia was seen only 10 times, and with a higher incidence in children than in adults, the adult disease more often being chronic lymphatic leukemia. There is a group of patients who show atypical leukemic pictures, often with recognizable sarcoma cells in the bone marrow and peripheral blood. The definition of this group is an arbitrary one and we have used the term leukolymphosarcoma for this category.

RESULTS OF THERAPY

The value of radiation therapy in the treatment of patients with lymphosarcoma is well established.[3,4,6,30] The comparative radiosensitivity of these tumors generally

TABLE II

FREQUENCY OF LEUKEMIC CHANGES IN PATIENTS PRESENTING INITIALLY WITHOUT LEUKEMIC CHANGES

| Initial Diagnosis | No. of Cases | Acute Leukemia | | Chronic Lymphatic Leukemia | | Leuko-lympho-sarcoma | | Total | |
|---|---|---|---|---|---|---|---|---|---|
| | | No. | Per Cent | No. | Per Cent | No. | Per Cent | No. | Per Cent |
| Giant Follicular Lymphosarcoma | 162 | 2 | 1.2 | 5 | 3.1 | 7 | 4.3 | 14 | 8.6 |
| Lymphosarcoma | 553 | 6 | 1.1 | 25 | 4.5 | 39 | 7.0 | 70 | 12.6 |
| Reticulum Cell Sarcoma | 554 | 2 | 0.4 | 4 | 0.7 | 7 | 1.3 | 13 | 2.4 |
| Total | 1,269 | 10 | 0.8 | 34 | 2.6 | 53 | 4.2 | 97 | 7.6 |
| Children | 69 | 5 | 7.2 | 0 | 0.0 | 4 | 5.8 | 9 | 13.0 |
| Adults | 1,200 | 5 | 0.4 | 34 | 2.8 | 49 | 4.1 | 88 | 7.3 |

permits some degree of symptomatic improvement, but it is not known whether this treatment has significantly prolonged survival.

Many other agents have been used and some have received enthusiastic support. At intervals, interest has been renewed in the possibility of surgical cure in certain localized forms of lymphosarcoma.[4,9,15,29]

It is difficult to compare the results of different forms of treatment in a chronic disease which has a highly variable natural history and for which there is no cure. No studies have been reported, nor is the present review an example, of a randomized, well-controlled, concurrently running analysis and comparison of different therapeutic regimens. However, an attempt has been made to study the therapeutic results observed during the thirty year period of this review.

Figure 3 shows the results obtained with the five agents used most frequently during the period of this study. By "complete" response is meant complete freedom from grossly detectable disease for a period of at least one month after the completion of, or while receiving, therapy. All other instances of objective regression, lasting for a period of at least one week without concomitant spread of disease eleswhere, were classified as "partially" benefited. If systemic therapy was given with irradiation, benefit was not attributed to the drug unless areas of disease not treated with radiation showed improvement.

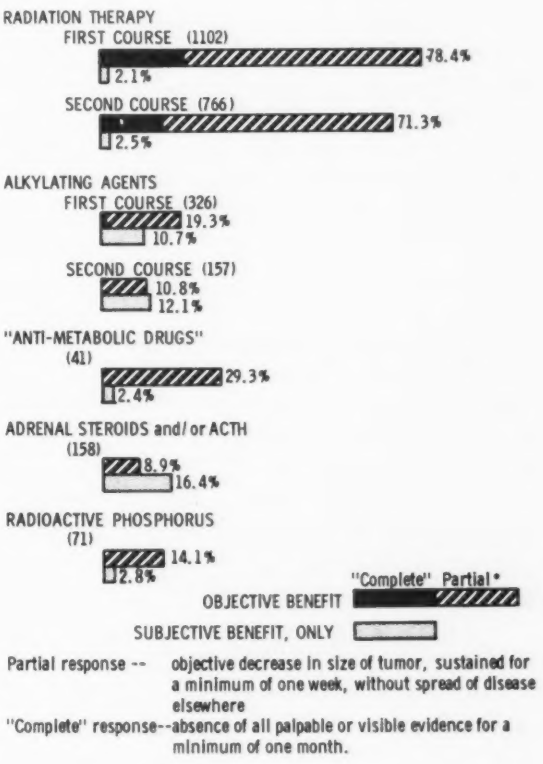


FIG. 3. Analysis of response to treatment of lymphosarcoma.

### RADIATION THERAPY

The first course of radiation therapy resulted in objective improvement in 78.4 per cent of the 1,102 patients treated; in over 20 per cent the benefit was classified as "complete." The second course of therapy gave almost equal results. In general, the same degree of response noted during the first course of radiation therapy was observed after the second. In most cases, the usefulness of radiation therapy was eventually limited by the generalized spread of the disease, by increased radioresistance of the tumor, and diminished tolerance of the patient.

### ALKYLATING AGENTS

Since the early 1940's, nitrogen mustard and related drugs have been extensively employed in patients with tumors of lymphoid origin.[5,13,18] Though several experimental agents were used in this series of patients, the great majority received either HN-2 (methyl-bis[beta-chloroethyl]-amine) or TEM (triethylene melamine).

Objective benefit, not attributable to simultaneously administered radiation, was observed in 19.3 per cent of patients after the first course of treatment, and in 10.8 per cent after the second. In only 2 instances did this improvement meet the criteria of complete benefit.

### ANTI-METABOLIC DRUGS

A total of 41 patients of this group received various folic acid or purine antagonists. Objective benefit, partial only, was recorded in 29.3 per cent. Ten patients had leukemic changes before the use of antimetabolic drugs. Seven of the 10 did not respond; the remaining 3 had a partial improvement.

### ADRENAL STEROIDS AND ACTH

Soon after it became known that stimulation of the adrenal gland or the administration of adrenal steroids had a deleterious effect on lymphatic tissue, these agents were used in the treatment of lymphosarcoma, with reported benefit in some patients.[21] In addition to their effects on the tumor, these agents may achieve symptomatic improvement, albeit temporarily, by suppressing pain and fever and by restoring in some measure lost weight, strength and a sense of well-being.

One hundred and fifty-eight patients received this type of therapy, the majority since 1950. Many of these patients had advanced disease and had received several courses of radiation therapy and antitumor chemotherapy. Though further chemotherapy in such cases was often contraindicated by hematopoietic depression, some form of treatment was demanded by continuing or recurrent constitutional symptoms. Adrenal steroids and ACTH were used most often in such patients in an attempt to improve the quality of their survival. In 8.9 per cent, partial benefit resulted. This benefit was objective, but usually brief, rarely lasting more than several weeks.

The patient with lymphosarcoma who develops a frank hemolytic anemia may be materially benefited by the use of adrenal steroids and ACTH, and sometimes temporary improvement is seen in the hemorrhagic manifestations of patients with profound thrombocytopenia.

### RADIOACTIVE PHOSPHORUS

The use of radioactive phosphorus in the treatment of lymphosarcoma initially received enthusiastic support, but it is now generally restricted to those patients showing the transition to chronic lymphatic leukemia.[7,19,20,23] Seventy-one patients with lymphosarcoma were treated with radioactive phosphorus during the period of this study, 14.1 per cent showing objective improvement.

### COMBINATION THERAPY

In certain situations, the intravenous administration of a rapidly acting alkylating agent immediately prior to radiation therapy is indicated. These are instances in which radiation therapy alone can aggravate the precarious state of patients with

TABLE III

CASES TREATED SURGICALLY

| Surgical Procedure | Giant Follicular Lymphosarcoma | Lympho-sarcoma | Reticulum Cell Sarcoma | Total |
|---|---|---|---|---|
| Neck Dissection | 2 | 6 | 11 | 19 |
| Axillary Dissection | 1 | 1 | 5 | 7 |
| Groin Dissection | | 1 | 1 | 2 |
| Supraclavicular Dissection | | | 1 | 1 |
| Gastrectomy | | 9 | 12 | 21 |
| Bowel and Lymph Node Dissection | | 2 | 3 | 5 |
| A-P Resection | | | 1 | 1 |
| Pelvic Exenteration | | 1 | | 1 |
| Head and Neck Procedure | | 2 | 4 | 6 |
| Amputation | | | 11 | 11 |
| Wide Skin Excision | 1 | | 1 | 2 |
| Total | 4 | 22 | 50 | 76 |

tumor compression of the superior vena cava, trachea or spinal cord. The alkylating agent seems to allow the use of larger and more frequent increments of radiation.

RADICAL SURGERY

We have evaluated the results of surgical attempts to eradicate lymphosarcoma. Such an evaluation should be interpreted with the realization that this is a retrospective study. These groups were not randomly selected and undoubtedly are not entirely comparable. Surgical procedures were usually attempted for only very early, well-localized disease. Seventy-six such procedures were accomplished in this group of patients and are summarized in Table III.

Table IV compares the end results and five year survivals of these patients with those who had the same extent of disease treated by nonsurgical methods, predominantly radiation therapy. These data indicate that the nonsurgically treated group with Stage I disease did significantly better

TABLE IV

COMPARISON OF RESULTS WITH SURGICAL AND NONSURGICAL MANAGEMENT

| | Stage I Lymphosarcoma | | Stage II Lymphosarcoma | |
|---|---|---|---|---|
| No. of Cases | 217 | | 396 | |
| % Treated with Surgery | 24% | | 6% | |
| | Surgery | Other Therapy | Surgery | Other Therapy |
| No. of Cases | 52 | 165 | 23 | 373 |
| End Results (per cent) | | | | |
| Dead of disease | 67.3 | 44.2 | 74.0 | 68.1 |
| Dead of ? | 5.8 | 10.9 | 4.3 | 10.4 |
| Lost, with disease | 5.8 | 2.4 | 0.0 | 4.6 |
| Lost, NED* | 7.7 | 12.7 | 13.0 | 3.0 |
| Alive, NED* | 13.5 | 21.2 | 8.7 | 5.6 |
| Five Year Survivals (per cent) | 28.8** | 52.2** | 13.0 | 23.9 |

* No evidence of disease for over one year.
** P equals less than 0.01.

TABLE V

ANALYSIS OF CASES WITH RADICAL NECK DISSECTION

| Case No. | Age | Sex | Diagnosis | Stage | Roentgen Therapy | Recurrence (mo.) | Duration (mo.) | End Result |
|---|---|---|---|---|---|---|---|---|
| 0734 | 41 | M | RCSA | II | No | Unknown | 1* | Dead of disease |
| 1045 | 11 | M | RCSA | II | No | 1 | 4 | Dead of disease |
| 1073 | 3 | F | LSA | I | No | 1 | 4 | Dead of disease |
| 0329 | 49 | M | LSA | II | No | 2 | 5 | Dead of disease |
| 1152 | 60 | M | RCSA | I | No | 1 | 7 | Dead of disease |
| 1146 | 13 | M | LSA | II | Yes | 2 | 10 | Dead of disease |
| 1164 | 50 | M | RCSA | I | Yes | 8 | 13 | Dead of disease |
| 0668 | 11 | M | RCSA | II | No | 4 | 16 | Dead of disease |
| 1166 | 52 | M | RCSA | I | No | 9 | 16 | Dead of disease |
| 0614 | 34 | M | RCSA | I | No | 10 | 17 | Dead of disease |
| 0659 | 51 | F | RCSA | I | No | 21 | 28 | Dead of disease |
| 1153 | 50 | F | LSA | I | No | Unknown | 38 | Dead of ? |
| 0932 | 58 | F | GFLSA | O | No | 24 | 80 | NED** |
| 1107 | 69 | M | LSA | I | No | 11 | 88 | Dead of disease |
| 1239 | 54 | M | RCSA | II | No | None | 93 | NED** |
| 1115 | 19 | M | LSA | II | Yes | 7 | 94 | Lost, NED** |
| 0951 | 40 | M | GFSLA | I | No | None | 168 | NED** |
| 1109 | 11 | F | RCSA | I | Yes | 17*** | 203 | NED** |
| 1116 | 40 | M | RCSA | I | Yes | 6 | 291 | NED** |

* Operative morbidity and mortality, with hemorrhage, nerve injury and pneumothorax.
** No evidence of disease for one year or more, at last evaluation.
*** Second partial radical neck dissection on opposite side for recurrent tumor, with postoperative roentgen therapy.
*Note:* RCSA = reticulum cell sarcoma; LSA = lymphosarcoma; GFLSA = giant follicular lymphosarcoma.

than those treated with surgery. The data are less conclusive in the groups with Stage II disease, though the tendency is again in favor of the nonsurgically treated patients.

The entire story, however, is not told from the over-all survival figures. Table V lists the 19 patients who underwent radical neck dissections. Six patients of this group have survived for long periods without evidence of disease. Three of these patients received radiation therapy to the surgically treated area, postoperatively. Of this group of 6 patients, the disease recurred in other sites in 4 instances from seven to twenty-four months after surgery. In 3 cases, radiation therapy has controlled the disease for periods of five to twenty-five years. The fourth patient underwent a partial radical neck dissection on the opposite side with postoperative irradiation and is now well over fifteen years later.

It is concluded from this analysis that radiation therapy remains the treatment of choice in this group of diseases because of the high degree of radiosensitivity of these tumors and the frequency of multicentric foci of lymphosarcoma in clinically well-localized disease.

### COMPLICATIONS OF THERAPY

In the final evaluation of any therapy, the frequency of serious complications (Table VI) must be compared to the expected frequency of benefit.

Of the 1,102 patients who received radiation therapy, 21, or 1.9 per cent, developed severe complications. These were radiation osteitis, persistent and severe radiation pneumonitis and fibrosis, severe skin ulcerations requiring plastic surgical repairs, severe iritis and glaucoma and aggravation of tracheal and superior vena cava obstruction.

The use of alkylating agents resulted in irreversible bone marrow damage in 3.1 per cent of those who received these drugs.

In addition, 2 patients who received nitrogen mustard developed severe uric acid nephropathy; 1 of these being fatal.

Bone marrow aplasia was encountered in 1 patient, or 2.4 per cent, of the group which received anti-metabolic drugs. Another patient, who was given four courses of 6-mercaptopurine, developed jaundice with each course of treatment, and at postmortem had extensive postnecrotic cirrhosis without tumor.

Adrenal steroids or ACTH were given to 158 patients in this series. A total of 16, or 10.1 per cent, developed complications thought to be directly related to this therapy. There were gastrointestinal ulcerations, usually unsuspected, overwhelming moniliasis or bacterial infections, moderate to severe psychoses, severe osteoporosis with fractures and aggravation of diabetes and congestive heart failure. These complications occurred despite the use of available preventive measures.

Ten, or 13.1 per cent, of the 76 patients who underwent radical surgery developed severe postoperative complications. In 8 of these instances, these complications appeared to be the direct cause of death.

Of the 71 patients who received radioactive phosphorus, 11, or 15.5 per cent, developed irreversible bone marrow depression or aplasia.

Table VI

FREQUENCY OF THERAPY COMPLICATIONS

| Therapy | No. of Cases | Complications (per cent) |
|---|---|---|
| Radiation | 1,102 | 1.9% |
| Alkylating Agents | 326 | 3.7% |
| Anti-Metabolic Drugs | 41 | 4.9% |
| Steroids and/or ACTH | 158 | 10.1% |
| Radical Surgery | 76 | 13.1% |
| $P^{32}$ | 71 | 15.5% |

### END RESULTS AND SURVIVAL CURVES

In order to evaluate the survival curves and to determine what differences, if any, can be shown to exist between various subgroups, the survival percentages have been plotted on log-probability paper, as shown in Figure 4. The data have been plotted as per cent survival after the clinical onset of disease as well as duration from the first Memorial Center visit. Plotted in this way, these data are linear over a wide range about the median and allow a better estimate of the median duration of disease than would be available from the crude data. The level of significance of difference between the two curves can be determined by applying the "t" test to differences in median survival, as determined from the most objective data, that is, from the duration of life after the first Memorial Center visit.[22,31]

Table VII shows the survival data for the various subgroups studied. All information was taken from survival curves as described above. The data from the clinical onset of disease shed some light on the natural history of lymphosarcoma in various settings. The data from the first Memorial Center visit are more accurate for statistical purposes and are comparable, one group to another. Yet, they do not describe the course of the disease, as the onset always antedated the first hospitalization

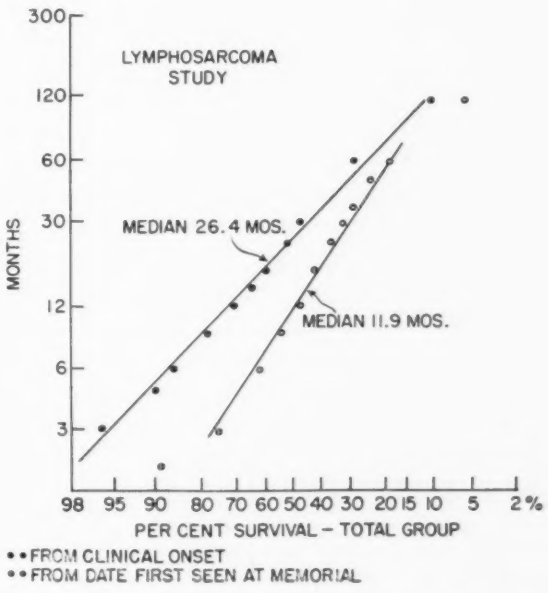


Fig. 4. Survival curves of 1,269 patients with lymphosarcoma. (Plotted on log-probability paper.)

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TABLE VII

VARIOUS COMPARISONS OF SURVIVAL DATA

| Groups Compared | No. of Cases | From Clinical Onset | | | From First Memorial Work-up | | |
|---|---|---|---|---|---|---|---|
| | | Two Years (per cent) | Five Years (per cent) | Median* (mo.) | Two Years (per cent) | Five Years (per cent) | Median* (mo.) |
| Total | 1,269 | 52.5 | 28.4 | 26.4 | 35.2 | 18.5 | 11.9 |
| Age | | | | | | | |
| 0–15 | 69 | 23.2 | 17.4 | 7.5 | 17.4 | 13.0 | 3.9? |
| 16–92 | 1,200 | 54.2 | 29.0 | 27.7 | 36.3 | 18.8 | 12.6 |
| Male | 790 | 50.4 | 26.5 | 24.2 | 34.4 | 17.3 | 10.5 |
| Female | 479 | 57.1 | 32.2 | 32.8 | 36.5 | 20.4 | 13.2 |
| Giant Follicular Lymphosarcoma | 162 | 85.2 | 54.4 | 72.0 | 64.8 | 33.9 | 48.0 |
| Lymphosarcoma | 553 | 51.3 | 27.0 | 25.2 | 35.8 | 18.6 | 11.7 |
| Reticulum Cell Sarcoma | 554 | 44.1 | 22.6 | 21.4 | 26.0 | 13.9 | 8.2 |
| Stage | | | | | | | |
| O–I | 245 | 66.3 | 46.6 | 51.0 | 55.7 | 40.7 | 34.5 |
| II | 397 | 44.9 | 23.2 | 22.2 | 30.8 | 17.7 | 10.5 |
| III | 627 | 52.0 | 24.5 | 25.5 | 30.0 | 10.4 | 8.4 |
| 1928–1934 | 95 | 53.1 | 29.2 | 26.8 | 34.8 | 17.9 | 12.8 |
| 1935–1939 | 122 | 57.8 | 34.7 | 28.7 | 42.7 | 26.2 | 18.1 |
| 1940–1944 | 274 | 53.3 | 29.6 | 27.8 | 36.2 | 22.6 | 13.2 |
| 1945–1949 | 385 | 47.6 | 26.0 | 22.6 | 34.6 | 19.5 | 10.6 |
| 1950–1952 | 309 | 51.8 | 25.9 | 26.6 | 36.8 | 15.5 | 11.4 |

* Medians from curves of all data were plotted on log-probability paper.

and the diagnosis in most cases was made prior to this date.

Certain observations concerning survival can be emphasized by the survival curves, as presented in Figures 5 through 9.

The disease in children is more rapidly fatal than in adults. Though 17.4 per cent of the children do survive five years or more, when the disease takes a downhill course, it does so at an accelerated rate.

As is well known, giant follicular lymphosarcoma is a much more benign disease than the other two groups. The group of patients with small cell lymphosarcoma survive slightly, but significantly, longer than the group with reticulum cell sarcoma.

It is interesting to note that female patients do somewhat better than male patients, as measured by survival rates. This is true for all age groups, but it is not evident for the group with giant follicular lymphosarcoma.

As would be expected, those patients with localized disease at the time of their first Memorial Center visit survive much longer than those with clinical Stage II or Stage III disease; however, the difference in survival between the latter two stages is not significant at the 5 per cent level.

Since the early 1940's new agents have been introduced for the treatment of lymphoid tumors. The alkylating agents, anti-metabolic drugs and adrenal steroid therapy have at one time or another received enthusiastic support. Great advances in blood replacement and the treat-

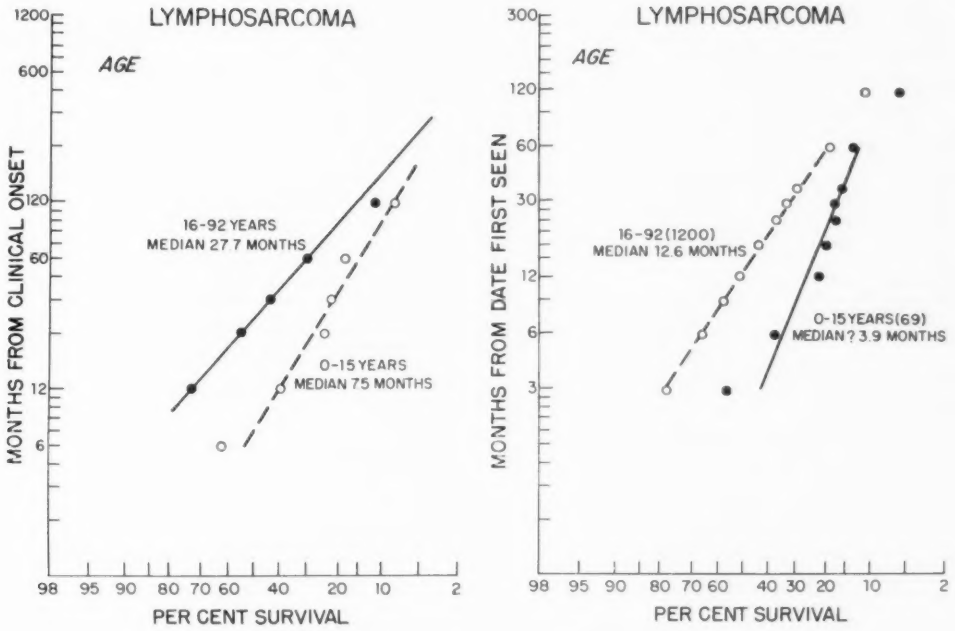


FIG. 5. Lymphosarcoma survival curves, children compared to adults.

ment of bacterial infections should have contributed to the longer survival of patients with lymphosarcoma.

Survival curves were analyzed as a function of the year of admission to Memorial Center. These curves (Fig. 9) indicate that no improvement in survival has resulted since 1928. Only the period from 1935 to 1939 stands out as showing better results than all periods before and after. Even this improvement is only slight. It is difficult to know whether changing diagnostic criteria

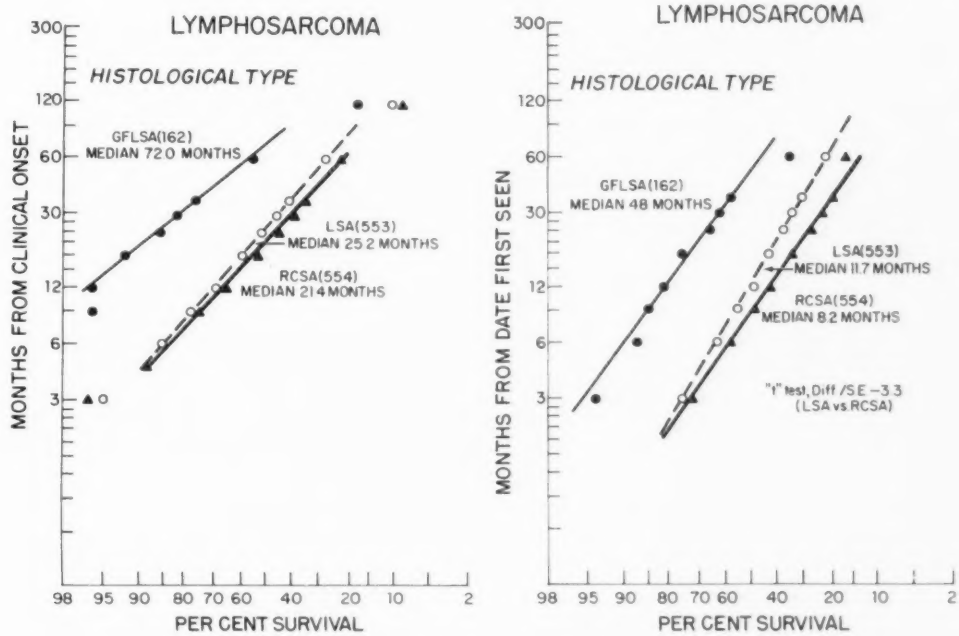


FIG. 6. Lymphosarcoma survival curves, histologic types compared.

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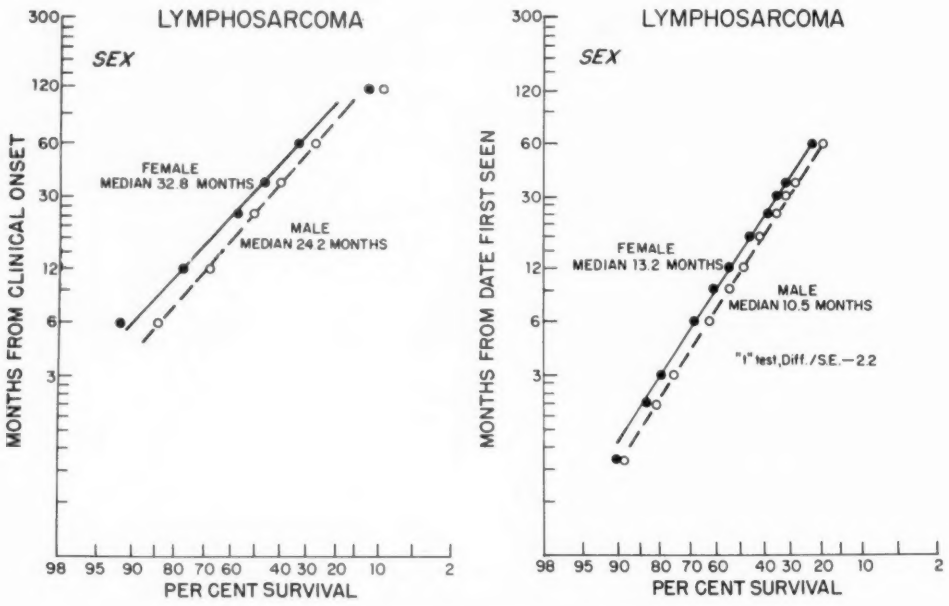


FIG. 7. Lymphosarcoma survival curves, male compared to female.

over the years or an increasing percentage of critically ill patients in recent years has influenced these results.

It is unfortunate that we have no group of nontreated patients to compare with those who received radiation therapy. However, it would appear that radiation therapy can provide as good results, measured by survival, as the newer agents introduced since 1940. Gross survival curves do not provide information concerning the quality of survival. We have all seen isolated cases of substantial improvement after the administration of the

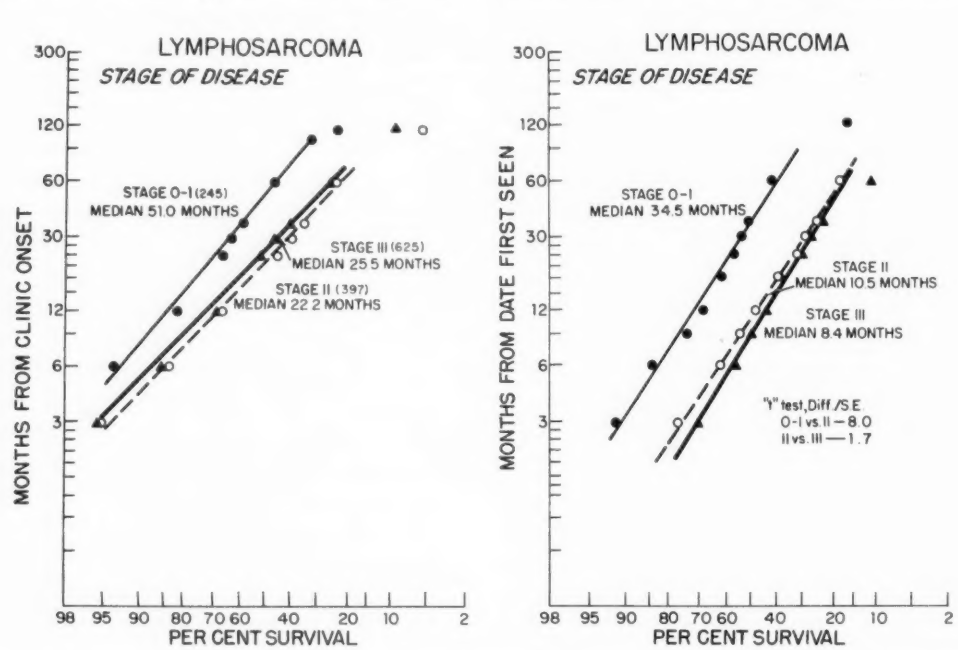


FIG. 8. Lymphosarcoma survival curves, comparison according to stage of disease on admission.

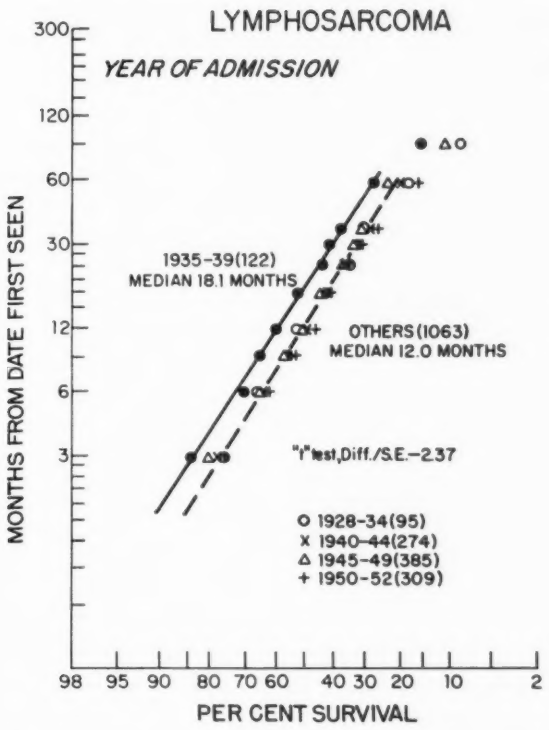


FIG. 9. Lymphosarcoma survival curves, comparison according to the year of admission to Memorial Center.

newer therapeutic agents. Specific problems such as superior vena cava obstruction and spinal cord compression undoubtedly respond more quickly and more safely with combination therapy than with irradiation alone. Therefore, we are not entirely justified in evaluating the new therapeutic agents on the basis of an analysis of gross survival data only.

## SUMMARY

A review has been completed of the experience at Memorial Center for Cancer and Allied Diseases with the group of diseases known generally as lymphosarcoma. All histologically proved cases were studied as of January 1, 1958, if they had been admitted to this institution between 1928 and 1953, thus providing a five year follow-up period.

Histologic diagnoses were divided into three groups: giant follicular lymphosarcoma, 162 cases; lymphosarcoma, 553 cases; and reticulum cell sarcoma 554 cases. Patients with manifest leukemia when first seen at this institution were excluded.

The age and sex distributions indicate a median age for the entire group of 49.7 years and a ratio of males to females of 1.7 to 1.0.

A leukemic transition was noted in 7.6 per cent of the entire group and was related to the patient's age and the histologic classification.

The objective and subjective response to treatment is presented for radiation therapy, 1,102 cases; alkylating agents, 326 cases; anti-metabolic drugs, 41 cases; adrenal steroids and/or ACTH, 158 cases; and radioactive phosphorus, 71 cases. The frequency of complications of therapy is also presented.

Seventy-six patients who underwent radical surgery are compared to those with comparable disease who received non-surgical treatment.

The over-all five year survival rate, from clinical onset, of patients with lymphosarcoma is 28.4 per cent. The median survival from clinical onset is 26.4 months. The survival figures as affected by the histologic group, age, sex, stage of disease, and year of admission are presented.

It is concluded that radiation therapy remains the treatment of choice for lymphosarcoma and that no increase in survival can be demonstrated over a period of twenty-five years, despite the addition of antibiotics, steroids, and alkylating agents to the therapeutic program of conventional radiation therapy.

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Vol. 85, No. 3

# SKIN AND SUBCUTANEOUS REACTIONS INDUCED BY SUPERVOLTAGE IRRADIATION*

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SUPERVOLTAGE gamma[25,34] and roentgen-ray radiations induce skin and subcutaneous reactions in far greater frequency and intensity than has been indicated in the literature.[5,9,17,27,31,32]

In contrast to the analyses in the past detailing skin reactions secondary to the use of conventional roentgen rays,[3,35] few papers describe and evaluate the skin reactions of high energy radiation.[5,8,9,27,31,32] Only general impressions on subcutaneous reactions have been published.[16,18,20,33]

The statement of Failla *et al.*[16] that "with higher dosages the limiting factor may become the tolerance of the subcutaneous tissue" is substantiated by the cases of subcutaneous fibrosis reported in this paper. They measured surface doses of supervoltage radiations with an extrapolation ionization chamber.[15]

The skin sparing characteristics of supervoltage therapy have been abundantly emphasized.[8,9,10,13,14,18,20,22,25,33,36] There are clinical reports of extensive supervoltage experience that practically disregard immediate superficial reaction.[4,13] One states that "no subcutaneous reaction at all has been met with in an extensive series over a five year period."[4]

The skin sparing of supervoltage radiation has come to mean spared skin in an absolute sense. We, on the other hand, have had supervoltage roentgen- and gamma-ray experience to the contrary and will attempt to place the matter of supervoltage integumental reactions in proper perspective by offering a detailed analysis. Unless the various factors[3,6,11,14,16,29,30,31,33] to be presented herein are included when reporting skin and subcutaneous reactions, the validity of the observations made can be challenged.

With the increased use of supervoltage modalities, fewer[5,9,10,23,31] rather than more[8,18,19,21] radiation equipment and surface dosage factors are found in publications, despite the abundant quantitative physical facts made available to us by the radiation physicists.[1,6,7,11,16,28,29,30,33]

The wider use and availability of the roentgen-ray generator and gamma-ray supervoltage equipment increase the need for knowledge of those factors which affect the design and performance of therapy machines in everyday practice. Therapy units that emit high energy gamma rays from cobalt 60 or cesium 137 sources should be designated as orthovoltage[34] if their design deviates from that of supervoltage equipment[6,24,33] which possesses skin sparing characteristics. These design deficiencies can be recognized and corrected.[9,31]

## REVIEW OF THE LITERATURE

Failla, Twombly, and Marinelli[16] in 1937 recognized that electron contamination of the air volume between the diaphragm system and the skin in supervoltage roentgen-ray therapy increased the superficial skin dose. They reasoned that, although superficial skin dose might be reduced by means of electron filtration, the tolerance of subcutaneous tissues might still become the limiting factor in higher dosage administration.

Quimby's[28] 1939 review of tissue dosage measurement emphasized the problem of tangential irradiation. There is no adequate

* From the Radiation Therapy Department, St. Luke's Hospital, New York. Presented at the Forty-second Annual Meeting of the American Radium Society, San Juan, Puerto Rico, March 17–19, 1960. Also presented as a scientific exhibit at the Sixty-first Annual Meeting of the American Roentgen Ray Society, Atlantic City, New Jersey, September 27–30, 1960 and at the Forty-sixth Annual Meeting of the Radiological Society of North America, Cincinnati, Ohio, December 4–9, 1960.



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measuring instrument for this troublesome factor in supervoltage irradiation. In the same paper Quimby states that the "tissue dose for tangential irradiations can not be properly obtained from isodose charts made with the beam of radiation entering the body at right angles, nor can the exit dose be obtained from such charts." She suggests that "although the discussion of tissue dosage was based entirely on the basis of physical measurements, it must not be lost sight of that biological questions are also exceedingly important." This is especially so when considering the variation of skin reactions based purely on anatomic site, tissue texture and skin sensitivities.[3]

Witwer and Leucutia[36] in 1940 evaluated the late sequelae of varying voltages on the skin. On the basis of limited experience with 600 kv. roentgen-ray therapy they concluded that "supervoltage roentgen therapy permits irradiation with the least damage to the skin, and therefore one may surmise that the danger of late sequelae may be entirely dismissed." This supposition did not refer to "heroic forms of protracted irradiation in which excessive cumulative doses are used."

Dresser, Rude, and Cosman[13] in 1940 evaluated the difference between 200 kv. and supervoltage one million volt therapy and concluded that with supervoltage irradiation not only were the immediate superficial reactions less intense but late skin damage in a two year experience had been entirely absent. They did remark, however, that a few cases developed "stiff erythemas," and they attributed the reaction largely to the exit dose.

In 1940, Stone and Robinson[32] compared the production of a similar skin reaction in the same patient induced by 200 kv. and 1,000 kv. radiations. To them, the important consideration was the reaction, not the number of roentgens measured. Thus, if biologically equivalent reactions are obtained from two different energies, the doses should be considered equivalent despite a numerical difference in roentgens measured. A dose, for Stone and Robinson, is the total skin dose, or the sum of "r on skin" ("r in air" plus backscatter) plus the exit dose. They hypothesized that, in producing a particular skin reaction, treatment by 1,000 kv. radiation may involve more roentgens as measured in air or by total skin dose than from 200 kv. radiation, but the doses would be considered equivalent. In fact, they concluded that, "allowing for biological inaccuracies, to produce similar skin reaction with these two qualities of radiation requires about 25 percent more total skin dose of the 1,000 KV. rays." Conversely, they pointed out that the same number of "r in air" from the two types of apparatus would result in less skin reaction from the 1,000 kv. rays than from the 200 kv. rays. The study of Stone and Robinson loses some value, however, since they used pressure cones with both the 200 and 1,000 kv. machines. These introduced effects on the skin due to pressure and electron contamination of unknown magnitude.

Trump and Cloud[33] in 1943 discussed the progressive movement of maximum ionization below the surface of the skin as the voltage increases, and they emphasized that the subcutaneous effect was already considerable for 1,000 kv. They stated that "the subcutaneous dose of maximum intensity should be taken as the measure of incident dose." The need for the use of sufficient air wall material overlying the Victoreen thimble chamber, to ensure measuring maximum ionization, is made clear.

In the same year, Dresser[12] discussed the bolus effect of low density material placed on the patient's skin. If the material is of sufficient thickness, *e.g.*, 5 mm. for 3,000 kv. roentgen rays, maximum ionization occurs directly on the skin. This effect, although generally to be avoided, can be used to advantage where the skin may be, or is, invaded by tumor.

Holmes and Schulz,[23] in 1946, reported on the use of 1,200 kv., Van de Graaff generated roentgen rays. They reaffirmed the com-

monly held viewpoint that supervoltage radiation was less likely to induce serious skin damage. Air doses, however, rather than total superficial skin or maximum subcutaneous doses per field were measured. Administering 6,000 r measured in air to single fields in head and neck cases, they observed that reactions were confined to the treated site of the neck and they reported no exit dose reactions.

In 1950, an additional basic article appeared by Murphy and Reinhard,[27] attempting to compare orthovoltage and supervoltage skin reactions. In their paper, an approach similar to that of Stone and Robinson[32] was used in that they directed 200 and 1,000 kv. roentgen rays to adjacent skin areas in the same patient but it differed in that they gave the same total skin dose per field (entry dose plus exit dose) each day, as well as for the total course and in the same over-all time. A total of 19 cases was included in the study. Thirteen patients, each treated simultaneously with both modalities, exhibited the same immediate skin reactions on the last day of treatment; in 3 cases the reaction was greater on the side treated with 1,000 kv., while in the other 3 cases the side treated with 200 kv. reacted more intensely. At the final observation four months later, sequelae were equal for the 200 and 1,000 kv. therapy in each of 10 patients, greater for the 1,000 kv. in 1 case and more pronounced for the 200 kv. in each of 7 other cases. They generally concluded that, in the same patient and for the same skin dose, the immediate reactions are equal for 200 and 1,000 kv. roentgen rays.

In 1952, Dixon, Garrett and Morrison[11] reported complete data on the Eldorado teletherapy $Co^{60}$ unit. (The same unit is used at St. Luke's Hospital, New York.) The most important facts they presented in reference to this supervoltage gamma ray equipment were the optimal source diaphragm distance and the optimal diaphragm skin distance. Both these factors give minimal penumbra and minimal electron contamination of the beam with maximum depth dose measurements. The supervoltage beam thereby produced is equivalent to that of a 3,000 kv. Van de Graff generator.

Miller[26] published depth dose measurements for a 2,000 kv. generator and showed that the dose delivered at a depth of 10 to 15 cm. is about ten per cent less than the dose delivered with cobalt 60 for the same maximum dose delivered in the skin.

Evans *et al.*[14] commented in 1954 on the Eldorado unit. They warned against the use of both closed- and open-end plastic applicators as they contribute electron contamination to the skin surface.

At St. Luke's Hospital, New York, the closed-end applicator on the Eldorado unit has never been employed.

Fried *et al.*[19] continued to use the Eldorado's closed-end applicator and resorted to rotational therapy to minimize skin reactions.

Haas, Harvey, and Laughlin[22] refer to the difference in average specific ionization as the important factor in 200 kv. versus higher kilovoltage skin effects.

Richardson, Kerman, and Brucer[30] in 1954 presented their evaluation of the effects of source skin distance, field size, cone inner lining and electron filters on the skin dose. They commented that for the same energy source, although the results should be similar, the actual measurements will vary with the design of the unit and the range of cone to skin distances.

The effect of closed-end applicators on the skin in supervoltage gamma therapy was presented in a paper published in 1954 by Burkell *et al.*[9] The skin reactions for the same field under open and closed parts of the applicator are shown in Kodachrome views. They observed that the skin reactions without closed-end applicators had been, in general, less pronounced than would have been expected with 200 kv. therapy. However, they included a photograph of a breast cancer patient who developed a moist skin reaction and deep pigmentation after a 4,000 r tumor dose administered in three weeks—a reaction

which can be considered severe even for 200 kv. therapy.

Friedman, Dresser, and Hine[20] in an article on 2,000 kv. roentgen-ray therapy also commented on the effects on the skin dose of target skin distance, electron emission from the collimating device and field size. They reported that with 8,000 r maximum skin dose delivered through a single portal, the only early skin reaction was a deceptively mild first degree erythema which healed rapidly. They did mention (without case presentation) that after using this dosage over a period of time severe radiofibrotic and radionecrotic effects will manifest themselves.

Fletcher *et al.*[17,18] pointed out in 1956 that, as with cobalt 60, the same optimal collimator-skin distance of 20 cm. also applies to a 2,000 kv. generator.[26] They cautioned, as others have, that subcutaneous fibrosis may occur. They also emphasized that the skin reaction on the exit side is as great as on the entry side and reported that, when using shorter collimator-skin distances without electron filters, moist desquamation had been observed.

Severe necrotizing skin reactions resulting from the use of cobalt 60 therapy machines with short collimator-skin distances are vividly demonstrated in a paper by Simon, Silverstone, and Gurman,[31] published in 1958, with their evaluation of the effectiveness of electron filters of different materials.

Burkell and Watson[8] in 1956 also pointed out the importance of eliminating closed-end applicators and avoiding the use of a bolus on the skin, if skin sparing is desired.

Baily and Beyer,[1,2] in 1957 and 1958, investigated the problems of surface and exit dose. They showed the significant variation of air dose rate and surface dose as a function of field size.

In 1959, Braestrup[6] presented the physical and Guttmann[21] presented the clinical advantages and limitations of cobalt 60 teletherapy. These two excellent papers give the essence of the factors which govern supervoltage gamma ray therapy. The authors also give the characteristics of units that have a short source-skin distance and short diaphragm distance. Except for the discussion by these authors on the influence of source size, all the other factors presented by them would apply equally as well to supervoltage roentgen-ray generators.

## MATERIAL

Twenty-three patients, 19 white, 4 Negro, with skin and subcutaneous reactions are reported in this paper. The skin changes are illustrative of the full range that may be met with in supervoltage therapy.

Between 1955 and 1959, 700 malignant cases were treated on the Eldorado telecobalt unit at St. Luke's Hospital, New York. Of these, 160 (22.8 per cent) showed some degree of integumental reaction. Included in the 160 cases are the 23 cases presented in this paper. Additionally, 2 patients (J.W. and J.C.) treated at Memorial Hospital, New York, are mentioned in the text with the kind permission of Dr. Ralph Phillips. One of us (L.L.) while at that institution was privileged to assist in the treatment of these 2 patients and at that time became interested in supervoltage skin reactions.

## IRRADIATION FACTORS

The St. Luke's Hospital Eldorado telecobalt unit conforms in design and performance to that described by Dixon *et al.*[11] Since the time of its original installation in 1954, and also at the present time, this unit has contained a cobalt 60 source 3 cm. in diameter with a half value layer of 1.1 cm. Pb.

Initially, the output at 80 cm. source skin distance was 44.5 r/min.; with the second source replacement made in December, 1957, the output was 57.6 r/min. at 80 cm. Monthly output corrections for decay are routinely made. The unit has been consistently operated with a source-diaphragm distance of 59 cm., a diaphragm-skin distance of 21 cm. and a source-skin distance of 80 cm. or 100 cm. for nonrota-

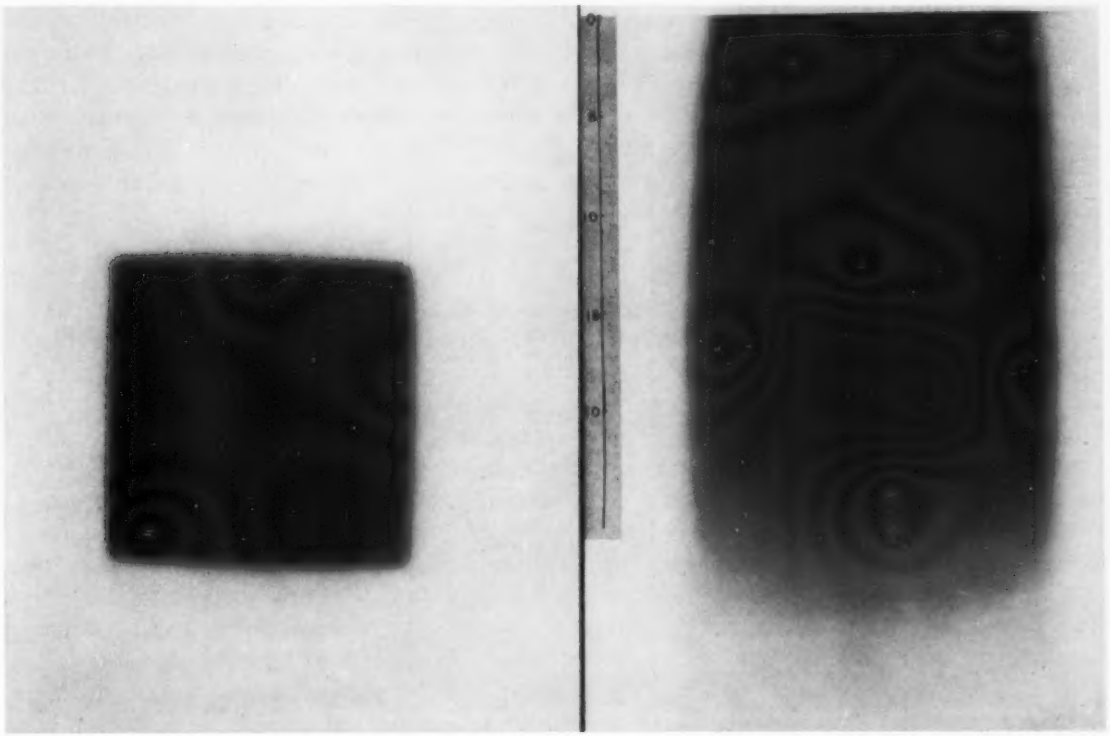

FIG. 1. Industrial type AA x-ray film exposed to a cobalt 60 beam in a large pressdwood phantom (SSD, 80 cm.; DSD, 21 cm.; FS, 15×15 cm.; source diameter, 3 cm.). The film is perpendicular to the beam axis (left) and parallel to the beam axis (right).

tional therapy. A light localizer with the mirror located near the source and fine wire cross hairs at the open face of the diaphragm aid in field centering. An open-end shaping platform with lead bars supported on the head of the machine outside of the field of irradiation is part of our auxiliary equipment but it was not employed in any of the cases reported in this paper.

All physical data for our unit relating to optimum diaphragm-skin distance, central axis depth doses, air dose rates, and surface and maximum dose rates for different field sizes at 80 and 100 cm. source distances were measured by one of us (N.M.). These determinations with slight variations confirm the results of Dixon *et al.*[11] As listed in Table II, the air dose rate as a function of field size varies significantly because of electron scatter from the variable diaphragm. The air dose rate increases to a maximum with our unit when a 15×15 cm. field size is attained, decreasing somewhat to a plateau thereafter. Enlarging the field size beyond 15×15 cm. apparently does not further increase the number of secondary electrons sufficiently energetic to be collected by an appropriate lucite capped Victoreen or Bomke ionization chamber. Similarly, the maximum dose and surface dose* vary with the field size.

The photographs in Figure 1 are of industrial type AA x-ray film, exposed in a large pressdwood phantom to the Eldorado telecobalt beam. We used a 15×15 cm. field to emphasize the uniformity of density across even a large field and the minimal penumbra present. With a densitometer we determined that the penumbra for such a large field is less than 1 cm. and for smaller fields is negligible. The latter was confirmed to our satisfaction clinically in cases where treatment was directed to the maxillary sinus in close proximity to the eye; sharp

* Surface skin dose refers to extrapolated values to zero thickness.

TABLE I

FACTORS INFLUENCING SKIN REACTIONS AND THE DIRECTION OF THEIR EFFECTS ON SKIN REACTIONS

| I. Physical | Physical (Continued) | II. Time-Dose Relationship | III. Skin | IV. Superimposed |
|---|---|---|---|---|
| A. Energy of Beam<br>Medium ↑<br>High ↓ | E. Scatter Effects<br>1. Entry<br>Underlying Bone ↑<br>2. Exit<br>a. Table<br>Metal ↑ ↑<br>Foam Rubber ↑<br>b. Table Dimension<br>Narrow ↑<br>Wide ↑ ↑ | A. Total Daily Dose per Field (entry+exit)<br>Low ↓<br>Medium ↓ ↑<br>High ↑ | A. Characteristics<br>Vascularity ↑<br>Texture<br>Fine ↑<br>Pigmentation ↓<br>Skin Thickness<br>Thin ↑<br>Sulfur Content<br>High ↑<br>Obesity ↑ | A. Prior Treatment<br>Irradiation ↑<br>Surgery ↑ |
| B. Diameter of Source<br>Small ↓<br>Large ↑ | F. Exit Dose<br>Low ↑<br>High ↑ ↑ | B. Total Number Treatments<br>Many ↓<br>Few ↑ | B. Anatomic Site<br>Scalp ↓<br>Neck ↓<br>Chest ↓<br>Abdomen (obese) ↑<br>Gr. in, Perineum, Axilla ↑<br>Extremities ↓ | B. Wound or Skin Infections ↑ |
| C. Equipment Design<br>1. Target or Source Skin Distance<br>Short ↑<br>Long ↓<br>2. Collimator (diaphragm)<br>a. Lining<br>High Atomic Number ↑<br>Medium Atomic Number ↓<br>b. Diaphragm Skin Distance<br>Short ↑<br>Long ↓<br>c. Cone (end)<br>Closed ↑<br>Opened ↓<br>3. Shaping Platforms ↑ | G. Angle of Incidence on Skin Surfaces<br>Direct ↓<br>Tangential ↑ | C. Over-all Time<br>Short ↑<br>Long ↓ | C. Skin Surface<br>Flat ↓<br>Curved ↑<br>Tangential ↑<br>Intertriginous ↑ | C. Applied Heat, Actinic Rays, and Chemicals ↑ |
| D. Bolus<br>Tissue or Tissue Equivalent ↑<br>Density >Tissue ↑ ↑ | H. Treatment Planning<br>Rotational ↓<br>Multiportal ↓<br>Parallel Opposing ↑<br>Single ↑ ↑ | D. Total Accumulative Dose per Field (entry+exit)<br>Low ↓<br>High ↑ | | D. Trauma ↑ |
| | I. Field Size<br>Small ↓<br>Medium ↑ ↑<br>Medium Large ↑ | E. High Dose Over Short Time ↑ | | E. Systemic Therapeutic Agents (actinomycin D) ↑ |
| | | F. High Dose Over Long Time ↑ ↓ | | F. Heightened Metabolic States ↑ |
| | | | | G. Gaseous Perfusions<br>Oxygen ↑<br>Nitrogen ↓ |
| | | | | H. Environmental Temperature<br>High ↑<br>Low ↓ |
| | | | | I. Anemia |

demarcations of skin reactions in these planned treatment fields are always observable. Depending upon the diaphragm system and source size of a given supervoltage unit, the maximum and skin doses for a given tumor dose will vary according to the design. Values could be greater, less than or the same as with our unit.

The last three columns of Table II, list the delivered total skin and maximum dose (entry+exit) per field and the total tumor dose attained in each case. The skin-tumor dose relationship remained favorable in every instance, even though parallel opposing fields were used. On the other hand, the maximum (0.5 cm. depth) dose exceeded or was equal to the tumor dose in all cases but 2, which we interpret as an unfavorable subcutaneous tissue-tumor dose relationship. No tumor dose administered in these cases exceeded 6,000 r.

Skin reactions induced by supervoltage radiation must be viewed in terms of the many factors listed in Table I.

Given the operative variables plus the possibility of their effects being additive, it would appear virtually impossible to avoid at least a minimal skin reaction, yet not all of our patients developed skin reactions. We believe, therefore, that our over-all incidence of 22.8 per cent for all gradations of skin reactions is realistic and valid.

If we are cognizant of even a few factors (such as electron contamination arising from short diaphragm-skin distance[30] and poor cone design[31] as well as the effect of

bolus material on the skin dose[22]), skin reactions may be kept to a minimum. The additive effects on the skin, however, of such adverse factors as an unfavorable time-dose relationship, skin site and physiology, as well as the other superimposed influences listed in Table I, may well outweigh any attempts we make at improving the physical features of a supervoltage unit.

Table II contains information routinely entered on our radiation therapy charts. The complete data include: half-value layer, source-skin distance, diaphragm-skin distance, applicator design, presence or absence of bolus material, field size, field arrangement, total individual number of treatments, daily and total cumulative skin and maximum doses (entry+exit), and the over-all time of the course of treatment.

Table II also shows the significant entry percentage skin doses, ranging from 35 per cent for smaller fields to 70 per cent of the maximum dose for fields of 300 cm.$^2$ or more. If parallel opposing fields are used, as they were in all our patients but 1, and if the interfield separation is small, as exemplified in head and neck cases, the percentage exit dose may be higher than the entry dose with exit dose values as high as 53 per cent.

The column headings in Table II designating "total daily skin and total daily maximum" doses have been devised by us to emphasize the entry and exit dose contribution per field to the skin and subcutaneous tissues from opposing fields treated alternately in each twenty-four hour period.

Field sizes varied depending upon the extent of the tumor and anatomic site. Small fields (30–150 cm.$^2$) were used in 6 patients; medium fields (150–300 cm.$^2$) in 10 patients; and large fields (300–420 cm.$^2$) in 7 patients.

The over-all time of the course of treatment expressed in weeks rather than days was: three weeks in 5 patients, four to seven weeks in 17 patients, and eight to nine weeks in 2 patients. (One patient had two courses of treatment separated by a three year interval.)

## REACTIONS

Skin reactions induced by supervoltage radiation as reported in this paper fall into two main categories: (1) those induced without bolus material intervening in the beam and without an unusual time dose relationship; and (2) those induced with bolus material intervening in the beam or with an unusual time dose relationship. These two categories are each further subdivided according to the type of reaction and the topography of the skin surface, *i.e.*, flat, curved (tangential), or intertriginous.

The first category contains 21 patients with the following number and types of reactions: erythema—flat surface, 3; follicular erythema—flat surface, 1; dry desquamation and tanning—flat surface, 2 (Fig. 2); moist desquamation—flat surface, 1; moist desquamation—intertriginous surface, 4 (Fig. 3); dry desquamation—tangential surface, 2 (Fig. 4); dry desquamation and late subcutaneous fibrosis—tangential surface, 1 (Fig. 5); and subcutaneous fibrosis—flat surface, 7 (Fig. 6, *A* and *B*).

One of the 4 patients with moist desquamation on an intertriginous surface (patient J.C.*) is not listed in our tables. Treatment factors were as follows: theratron $Co^{60}$ machine, 360° horizontal rotation and an 8×12 cm. field for an over-all time of forty-two days and a total tumor dose of 6,000 r. Severe moist desquamation began with a 4,000 r tumor dose accumulated in thirty days.

The second main category contains 4 patients with the following reactions: follicular tanning—flat surface, 1 (patient R.N., Table II); moist desquamation—intertriginous surface, 1 (patient F.P., Table II; moist desquamation—bolus, 2 (patient W.St.C., Table II and Dr. Phillips' patient, J.W.).

Since patient J.W.* is not listed in our

* These patients were treated at Memorial Hospital, New York, and are included with the permission of Dr. Ralph Phillips.

## Table II

FACTORS OF COBALT 60 IRRADIATION

(SOURCE-SKIN DISTANCE—80.0 cm., DIAPHRAGM-SKIN DISTANCE—21.0 cm., SOURCE DIAMETER—3.0 cm.)

| Site | Patient | Over-all Time (days) | Field Size (cm.) | Fields | Air Dose Rate (r/min.) | Skin Dose (per cent) | Max. Dose (per cent) | Exit Dose (per cent) | Daily Skin Dose per Field | | | Daily Maximum Dose per Field* | | | Final Total Dose per Field (entry+exit) | | Tumor Dose (r) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | Entry Dose (r) | Exit Dose (r) | Total Dose (r) | Entry Dose (r) | Exit Dose (r) | Total Dose (r) | Skin Dose (r) | Max. Dose (r) | |
| Head and Neck | W.M. | 38 | 5× 6 | // opposed | 43.3 | 35.0 | 100 | 51.5 | 106 | 157 | 263 | 304 | 156 | 460 | 3,400 | 6,000 | 6,000 |
| | J.Mc. | 42 | 5× 6 | // opposed | 42.6 | 35.0 | 100 | 52.7 | 91 | 137 | 228 | 260 | 137 | 397 | 4,200 | 6,000 | 6,000 |
| | L.C. | 41 | 5× 6 | // opposed | 47.2 | 35.0 | 100 | 51.0 | 91 | 133 | 168 | 261 | 133 | 394 | 3,400 | 6,000 | 6,000 |
| | G.K. | 43 | 5× 6 | // opposed | 42.6 | 35.0 | 100 | 52.5 | 91 | 137 | 228 | 262 | 137 | 399 | 4,300 | 6,200 | 6,000 |
| Supraclavicular | J.M. | 43 | 11×11 | // opposed | 46.5 | 50.0 | 104 | 40.0 | 148 | 118 | 266 | 296 | 118 | 414 | 3,900 | 5,900 | 4,600 |
| | A.M. | 42 | 15×15 | // opposed | 47.0 | 63.0 | 105 | 50.0 | 159 | 133 | 292 | 266 | 133 | 399 | 4,400 | 6,000 | 6,000 |
| | M.P. | 22 | 10×20 | // opposed | 46.7 | 62.0 | 102 | 42.0 | 220 | 150 | 370 | 350 | 124 | 474 | 2,700 | 3,800 | 3,700 |
| | C.O. | 35 | 12×15 | Single, direct | 53.2 | 60.0 | 104 | 40.0 | 153 | 102 | 355 | 255 | — | 255 | 3,800 | 6,400 | 5,000 |
| Chest-Axilla | H.P. | 44 | 17×22 | // opposed | 50.0 | 70.0 | 106 | 27.0 | 240 | 93 | 333 | 344 | 93 | 437 | 5,000 | 6,600 | 6,000 |
| | P.G. | 46 | 15×26 | // opposed | 44.4 | 70.0 | 106 | 25.0 | 250 | 96 | 346 | 385 | 96 | 481 | 5,200 | 6,200 | 6,000 |
| Breast | W.St.C. | 27 | 12×18 | // opposed, tangential, bolus | 48.5 | 64.0 | 105 | 22.0 | 256 | 88 | 344 | 400 | 88 | 488 | 3,400 | 4,800 | 4,000 |
| | A.K. | 28 | 13×17 | // opposed, tangential, no bolus | 54.2 | 64.0 | 104 | 30.0 | 220 | 100 | 320 | 344 | 103 | 447 | 3,200 | 4,500 | 4,000 |
| Abdomen | H.A. | 35 | 15×15 | // opposed | 51.0 | 64.0 | 102 | 15.0 | 332 | 64 | 396 | 520 | 64 | 584 | 3,600 | 5,900 | 4,000 |
| Pelvis | F.P. | 19 | 20×18 | // opposed | 45.0 | 70.0 | 106 | 15.0 | 500 | 105 | 605 | 700 | 105 | 805 | 3,900 | 5,300 | 4,100 |
| | A.N. | 1. 24 (3 yr. interval) | 12×12 | Four // opposed | 53.0 | 51.0 | 102 | 10.0 | 195 | 40 | 235 | 379 | 38 | 407 | 2,000<br>2,500 | 3,900<br>5,000 | 4,700<br>4,300 |
| | | 2. 31 | 9×12 | Four // opposed | 55.5 | 55.0 | 103 | 10.0 | 165 | 38 | 203 | 383 | 38 | 421 | 4,500 | 8,900 | 9,000 |
| | I.S. | 60 | 14×15 | Four // opposed | 55.6 | 63.0 | 105 | 20.0 | 350 | 110 | 460 | 550 | 110 | 660 | 3,500 | 5,300 | 6,000 |

| Site | Patient | Over-all Time (days) | Field Size (cm.) | Fields | Air Dose Rate (r/min.) | Skin Dose (per cent) | Max. Dose (per cent) | Exit Dose (per cent) | Daily Skin Dose per Field | | | Daily Maximum Dose per Field* | | | Final Total Dose per Field (entry+exit) | | Tumor Dose (r) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | Entry Dose (r) | Exit Dose (r) | Total Dose (r) | Entry Dose (r) | Exit Dose (r) | Total Dose (r) | Skin Dose (r) | Max. Dose (r) | |
| | E.D. | 37 | 18×15 | // opposed | 51.3 | 65.0 | 105 | 30.0 | 234 | 108 | 342 | 360 | 108 | 468 | 4,300 | 5,600 | 5,000 |
| | G.K. | 39 | 21×15 | // opposed | 46.0 | 68.0 | 106 | 30.0 | 198 | 90 | 288 | 302 | 90 | 392 | 4,100 | 5,600 | 5,000 |
| | R.N. | 19 | 14×13 | // opposed | 45.5 | 60.0 | 105 | 35.0 | 400 | 140 | 540 | 600 | 175 | 775 | 3,000 | 4,300 | 4,000 |
| | L.F. | 40 | 22×19 | // opposed | 45.0 | 70.0 | 106 | 20.0 | 296 | 85 | 381 | 424 | 85 | 509 | 4,000 | 5,600 | 4,300 |
| | R.B. | 30 | 20×20 | // opposed | 48.5 | 70.0 | 106 | 30.0 | 240 | 115 | 355 | 345 | 104 | 449 | 3,500 | 4,000 | 4,0000 |
| | J.M. | 55 | 22×14 | // opposed | 49.5 | 70.0 | 104 | 25.0 | 264 | 95 | 359 | 378 | 95 | 473 | 5,000 | 6,100 | 6,000 |
| Hip | L.G. | 23 | 11×15 | // opposed | 45.8 | 59.0 | 104 | 28.0 | 260 | 121 | 381 | 440 | 121 | 561 | 2,200 | 4,800 | 4,000 |

* At 0.5 cm. depth.



FIG. 2. Patient P.G. Photograph taken fourteen days after the last treatment shows marked tanning and marked dry desquamation. A superficial skin dose (entry+exit) of 5,200 r was administered through 15×26 cm. parallel opposing fields in an over-all time of forty-six days. No bolus was used. This is an example of a reaction on a flat surface.



FIG. 3. Patient H.P. Photograph taken at the end of therapy shows marked erythema and moist desquamation in the right axilla. A superficial skin dose (entry+exit) of 5,000 r was administered through 17×22 cm. parallel opposing fields in an over-all time of forty-four days. No bolus was used. This is an example of an intertriginous reaction.

FIG. 4. Patient C.O. Photograph taken four days after the end of therapy shows marked dry desquamation and tanning. This view shows the exit side of a single 12×15 cm. anterior supraclavicular-axillary field. Superficial skin dose (entry) 3,800 r, exit dose (without backscatter) 2,500 r, maximum dose 6,400 r. The dose was delivered in an over-all time of thirty-five days in 25 individual treatments. This is an example of tangential skin and exit dose effects.

FIG. 5. Patient A.K. Photograph taken eight months after completion of therapy shows marked subcutaneous fibrosis following medial and lateral parallel opposing tangential irradiation of primary inoperable breast cancer No bolus was used A skin dose (entry+exit) of 3,200 r and a maximum dose (entry+exit) of 4,500 r were delivered through 13×17 cm. fields in an over-all time of twenty-eight days. Erythema was present at the completion of the course and there was marked dry desquamation three months later. The adjacent rectangular reaction was secondary to 140 kv. therapy. This is an example of subcutaneous fibrosis following tangential irradiation.

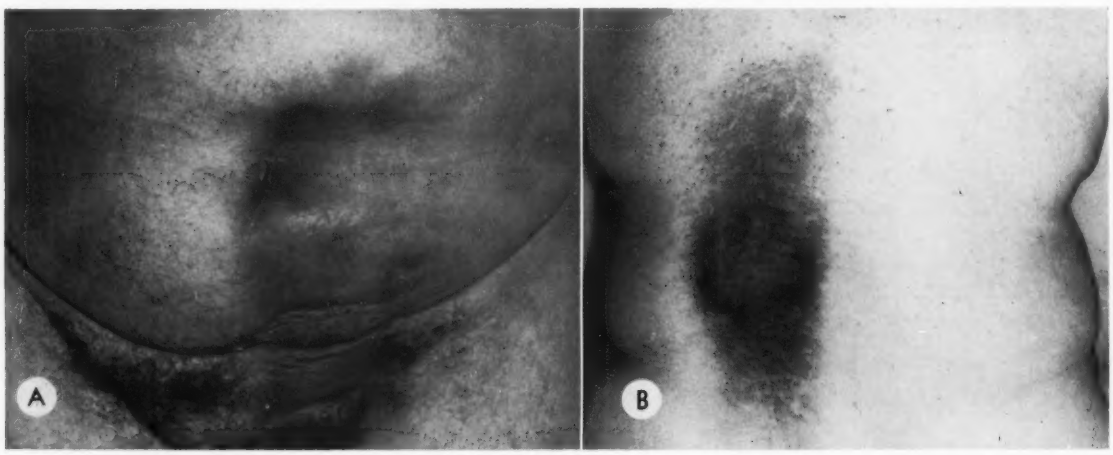


FIG. 6. (*A*) Patient H.A. Photograph taken thirty-three months after the last treatment shows very severe, retracted, pigmented, brawny-hard subcutaneous fibrosis of the anterior abdominal-pelvic wall. A maximum subcutaneous dose (entry+exit) of 5,900 r was delivered through upper and lower 15×15 cm. parallel opposing fields (superficial skin dose 3,600 r) in an over-all time of thirty-five days in 25 individual treatments. Reaction occurred only in the more midline portions of the field irradiated. This was first observed three and one-half months after the completion of therapy. (*B*) Same as *A* showing subcutaneous fibrosis over the posterior portals. The reaction in this patient is an example of severe subcutaneous fibrosis.

TABLE III

ANALYSIS OF SKIN AND SUBCUTANEOUS REACTIONS INDUCED BY SUPERVOLTAGE (COBALT 60) IRRADIATION

| Site | Patient | Early Reactions: Erythema | Erythema and Tanning | Tanning | Desquamation and Tanning | Moist Desquamation—Flat Surface | Moist Desquamation—Intertriginous Surface | Late Reactions: Subcutaneous Fibrosis: Without Inflammation | Late Reactions: Subcutaneous Fibrosis: With Inflammation | Total Dose per Field (entry + exit): Skin Dose (r) | Total Dose per Field (entry + exit): Subcutaneous Dose (r) | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Head and Neck | W.M. | ++ | | | | ++ | | | | 3,400 | 6,000 | |
| | J.MC. | ++ | | | | | | | | 4,200 | 6,000 | |
| | L.C. | + | | | | | | | | 3,400 | 6,000 | |
| | G.K. | + | | | | | | | | 4,300 | 6,200 | |
| Supraclavicular | J.M. | | ++ | | ++ | | | | | 3,900 | 6,000 | Tangential effects |
| | A.M. | | | ++ | +++ | | | | | 4,400 | 6,000 | |
| | M.P. | | | | | | | + | | 2,700 | 3,800 | |
| | C.O. | + | | | +++ | | | | | 3,800 | 6,400 | Tangential effects |
| Chest | H.P. | + | ++ | | | | ++ | | | 5,000 | 6,600 | Chest wall, axilla |
| | P.G. | | + | | +++ | | | | | 5,200 | 6,200 | |
| Breast | W.St.C. | + | | | | | +++ | | | 3,400 | 4,800 | Bolus |
| | A.K. | + | | | ++ | | | +++ | | 3,200 | 4,500 | No bolus |
| Abdomen | H.A. | | | | | | | | ++++ | 3,600 | 5,900 | Very obese |
| Pelvis | F.P. | +++ | | | | | +++ | | | 3,900 | 5,300 | |
| | A.N. | | | | | | | | ++ | 4,500 | 8,900 | 2 courses, 3-yr. interval |
| | I.S. | | | | | | ++ | | +++ | 3,500 | 5,300 | Obese |
| | E.D. | | | ++ | ++ | | | +++ | | 4,300 | 5,900 | Thin abdomen |
| | G.K. | + | | | ++ | | + | | | 4,100 | 5,600 | |
| | R.N. | | +++ | | | | | | | 3,000 | 4,300 | |
| | L.F. | ++ | | | | | ++ | | | 4,000 | 5,600 | Very obese |
| | R.B. | + | | | | | | ++ | | 3,500 | 4,000 | |
| | J.M. | ++ | | | | | | +++ | | 5,000 | 6,000 | |
| Extremities | L.G. | +++ | | | | | | | | 2,200 | 4,800 | Follicular reaction |

Reactions: 18 erythema (with or without tanning); 9 tanning (with or without desquamation); 7 moist desquamations; 8 subcutaneous fibrosis.

tables, a brief résumé of the case follows: Treatment was with a 1,000 kv. General Electric Resonant transformer with a focal skin distance of 70 cm., half value layer of 3.7 mm. Pb, parallel opposing 18×12 cm. fields, with the beam passing through a 1.5 cm. thick, circular plaster cast. Twenty-eight days after initiation of therapy, a window was made in the cast overlying the treatment field exposing a most intense, violaceous, vesicular, moist desquamation. The Victoreen and Baldwin-Farmer chamber readings indicated a superficial skin dose in the presence of a plaster bolus of 4,400 r (entry dose plus exit dose) delivered in an over-all time of twenty-eight days. Dr. Arvin Glicksman (Memorial Hospital, New York) was responsible for the triiodothyronine therapy that was effective in inducing rapid skin healing in this patient.

Table III lists the intensity of each type of reaction. Early reactions refer to those evident during therapy and in the immediate post-treatment interval. Late reactions refer to those occurring at least one month after treatment. Patients have demonstrated either a single isolated reaction or a sequence of multiple reactions that proceeded to healing.

In the 23 patients listed, 18 erythematous reactions (in 17 patients) were observed, 14 of which were erythema alone,

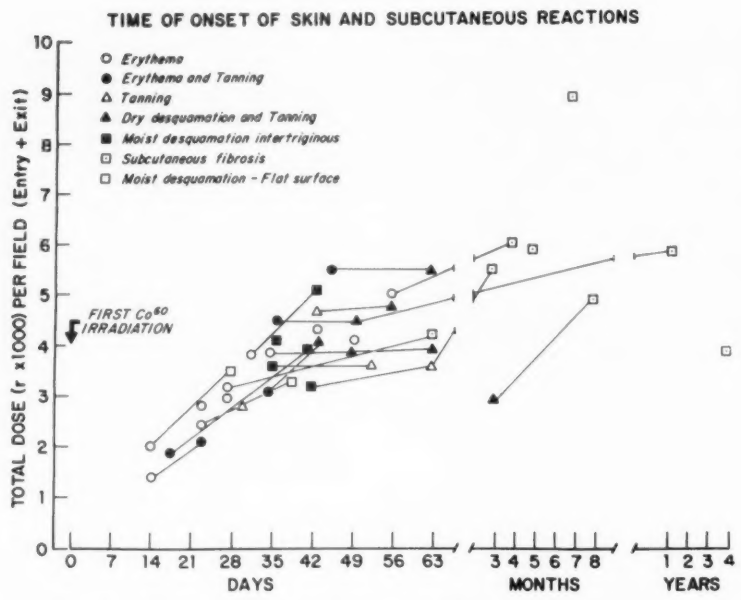


Fig. 7. Graphs showing the time of onset of skin and subcutaneous reactions.

with tanning occurring simultaneously in 4. There were 9 tanning reactions; 7 of these were accompanied by dry desquamation. Only 1 instance of moist desquamation on a flat surface was observed; a bolus was not used on this patient. Six instances of moist desquamation in intertriginous areas were recorded.

There were 8 late subcutaneous fibrotic reactions, 6 in the abdominal-pelvic or lumbar area and 1 each in the breast and sternal areas. Of the 8 subcutaneous reactions, 3 were accompanied by intense inflammation (patient I.S. had a superimposed low grade abdominal wound infection).

In evaluating supervoltage skin and subcutaneous reactions from the aspect of the anatomic site irradiated, our analysis reveals that 12 patients are in the head and neck, supraclavicular, chest, and breast groups; they demonstrated 20 early skin reactions and 2 late subcutaneous fibrotic reactions. The main features these cases had in common were curved skin surfaces, smaller interfield separation and, consequently, higher exit doses. In the 11 other patients where treatment was directed to the abdomen, pelvis, or extremities, 14 early skin reactions and 6 late subcutaneous fibrotic reactions were noted. All of these 11 patients were obese; they had healed or healing abdominal incisions; there were large interfield separations; and the treated skin surfaces were intertriginous.

Figure 7 shows the time of onset of various skin and subcutaneous reactions on three different time scales. The mildest skin reactions did not occur earlier than two weeks after the start of irradiation, appearing within a range of fourteen to fifty days. The majority of these first reactions became evident between twenty-one and forty-two days after the initiation of treatment. Erythema may be present as the earliest and only reaction (Fig. 7). Similarly, tanning, dry desquamation, moist intertriginous changes and subcutaneous fibrosis may appear without milder preceding reactions. The classic sequence of skin changes described for lower voltage therapy is not always evident in supervoltage therapy. Five of the 8 subcutaneous fibrotic reactions were accompanied only by erythema or were not preceded by any skin change at all.

Excluding subcutaneous reactions, the interval between the earliest skin reactions

and fully developed reactions was two to three weeks in most cases. The interval between the fully developed reaction and healing was generally two weeks. In 4 cases, however, complete healing required one to three months, calculated from the time of appearance of the maximum reaction. The total time interval, therefore, between the first appearance of the earliest reaction and final skin healing ranged between two and four months.

Subcutaneous fibrosis, measured from the time of the first treatment, developed in 1 case at two months, in 5 cases between two and seven months, and in 2 cases at one year and four years, respectively (Fig. 7).

The earliest reactions appeared at skin doses of 500 to 1,500 r below the final administered skin dose in 10 cases (approximately 40 per cent) of the total of 23 reported. In 6 cases (approximately 25 per cent of the 23 reported) the earliest reactions first appeared when the total skin dose (entry+exit) had been administered, becoming a fully developed reaction thereafter. Fully developed skin reactions in most patients first appeared only after the administration of the total skin dose (entry +exit).

Figures 7 and 8 are based on reactions induced by supervoltage radiation without the use of an intervening bolus (except case W.St.C., advanced breast cancer invading the axilla and skin of the breast) or an unusual time dose relationship (except cases R.N. and F.P.).

Figure 8 plots the final fully developed maximum skin and subcutaneous reactions relative to total skin and maximum dose (entry+exit) delivered and to field area in square centimeters. We were able to define three fairly distinct reaction groups in which a dose to field area relationship seems apparent.

For smaller fields (30–180 cm.$^2$), total skin doses (entry+exit) ranging between 3,500 r and 4,500 r generally may be given without a reaction greater than erythema and tanning. (Case W.M. is an exception, Table II.)

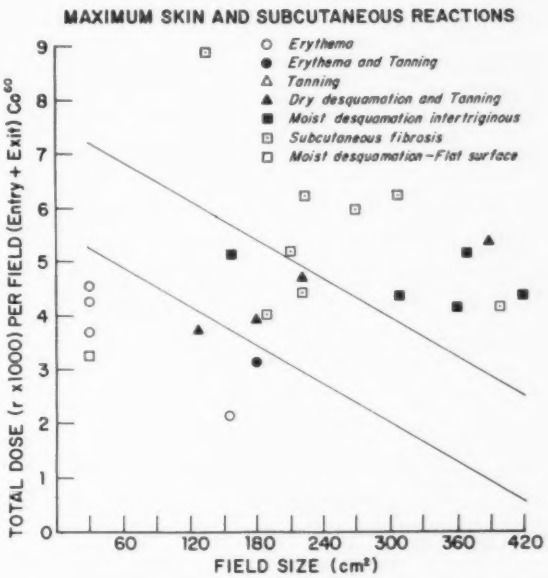


FIG. 8. Graphs showing maximum skin and subcutaneous reactions.

For moderately sized field areas (150–210 cm.$^2$), total doses (entry+exit) ranging between 3,800 r and 5,300 r delivered to abdominal-pelvic sites will result in more intense reactions, including some cases of subcutaneous fibrosis.

With larger field areas (230–420 cm.$^2$) and with total doses (entry+exit) ranging between 4,000 r and 6,500 r, a markedly increased incidence of more intense skin and subcutaneous fibrotic reactions can be expected, especially in the abdominal-inguinal-perineal intertriginous areas.

In 1 case subcutaneous fibrosis occurred four years after the first course of therapy and after an accumulated dose of 8,900 r, with an interval of three years between the two courses of therapy (case A.N., Table II).

We have observed no instance of an acute skin reaction failing to heal. Radiation ulceration or necrosis of the skin has not occurred in any of the 700 cases treated by us with telecobalt therapy.

Of the acute supervoltage skin reactions, intertriginous moist desquamation represents the greatest problem to the therapist. Particularly troublesome are reactions oc-

curring in the axillary, inguinal, perineal and perianal areas. This complication is painful and distressing to the patient. It may require discontinuance of therapy, preventing the delivery of a proper cancericidal dose. These intertriginous reactions are in no way limited to stationary field therapy. Some of the most intense and painful reactions have occurred during horizontal rotational therapy (Dr. Phillips' patient J.C.).

## DISCUSSION

The mechanisms which may cause these intertriginous reactions are related to the physics of supervoltage ionizing radiation and the physiology of the intertriginous skin surfaces, especially in the inguinal-perineal area. One can readily observe in all patients an increased pigmentation in these areas, which suggests a unique physiology and per haps an altered sulfur content. This pigmentation is intensified both with conventional and supervoltage roentgen rays so that the higher reactivity in these areas must be related to ionizing radiation, irrespective of quality. The increased ionization in skin surfaces, due to the tangential incidence of photons and the bolus effect of opposed skin surfaces, causes heightened reaction in these intertriginous zones, whereas the same calculated skin dose delivered to adjacent flat surfaces is not usually associated with a skin reaction.

In horizontal 360° rotational therapy this also happens. As an example, in patient J.C. the buttock skin hyper-reacted while the anterior suprapubic skin, although also reacting, was remarkably less affected. The treatment table on which the patient lay acted as a bolused surface so that during part of the rotation, when the photons were directed from underneath the table, electron equilibrium attained maximal value in the table thickness and continued thereafter onto the skin of the buttock.

One of us (L.L.), in 1956, suggested that of the two factors, bolus and tangential effects, the tangential incidence of photons was more significant in producing moist reactions in intertriginous zones, such as the inguinal-vulval-perineal areas. This was based on the observation that heightened erythemas occurred on the lateral chest wall without bolus, when the beam incidence was tangential to such a curved surface. In order to substantiate this observation, skin dose rates (Table IV) were measured with chambers placed at tangential and intertriginous perineal surfaces, with and without a bolus. These measurements corroborated the prediction that tangential skin surfaces would receive a lower dose rate if they were incorporated into a bolused volume. We recognized, however, that the increased softer scatter from the adjacent bolus might outweigh the apparent advantage of eliminating the additive dose resulting from maximum ionization building up in the superficial skin parallel to its surface, as the incident photons penetrate tangentially.

Subsequent to these measurements, all curved surfaces (axilla, chest wall and vulval-perineal area) were filled in with an appropriate number of bolus bags in patients under our care. As a general rule, at the present time we do not use a bolus in this fashion. We individualize, however, in the use of a bolus depending on the obesity, pigmentation and field placement. Routinely, we attempt by the use of proper pillow support to keep irradiated surfaces perpendicular to the incident beam.

Contrary to the report of Murphy and Reinhard,[27] we believe that, for the same total skin dose per field, delivered to the same anatomic site through the same field size and for the same time dose interval, supervoltage radiation induces substantially less reaction than conventional orthovoltage roentgen rays, despite the occurrence of severe intertriginous moist reactions and subcutaneous fibrosis.

The relative skin sparing of supervoltage radiation compared to 200 kv. roentgen rays is dramatically evident when large field therapy is employed. The most intense reaction observed by us on a flat surface

TABLE IV

SURFACE DOSE RATES

| Tangential Surfaces | Modality | Field Size (cm.) | TSD or SSD (cm.) | Air Dose Rate (r/min.) | Type of Chamber Used | Readings (r/min.) | | Calculated Dose (r/min.) | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | No Bolus | Bolus | No Bolus | Bolus |
| Lateral chest wall | 1 mev. | 22×23 | 100 | 43.5 | Victoreen | 43.5 | 37.7 | 41.5 | 39.5 |
| Lateral breast | 1 mev. | 31×23 | 100 | 46.5 | Victoreen | 44.0 | 41.0 | 52.0 | 52.0 |
| Perineum | $Co^{60}$ | 10× 6.8 | 75 | — | Victoreen | 10.0 | 8.4 | — | — |
| Lateral hip | $Co^{60}$ | 15×15 | 80 | 44.0 | Bomke { 4 mm. cap | 33.6 | 25.2 | 34.8 | 23.0 |
| | | | | | Bomke { no cap | 29.4 | 24.2 | | |
| Flat Surface | 1 mev. | 18×12 | 70 | 87.0 | Victoreen | — | 70.5 | — | |
| Anterior thigh* | | | | | Baldwin-Farmer | | 71.3 | | 80.9† |

* Overlying plaster cast 1.5 cm. thick.
† Based on soft tissue bolus.

occurred in a patient (Case P.G., Table II and Fig. 2) in whom a total superficial skin dose of 5,200 r was delivered to a skin area of 390 cm.$^2$ over a usual time interval. His skin reacted with intense tanning and marked dry desquamation. Had this same dose been delivered to a similar area with 200 kv. roentgen rays, a most severe necrotizing moist desquamation would have resulted.

We urgently caution the reader against applying the dosage information and resulting skin reactions reported in this paper to therapy with cobalt 60, cesium 137, or other future gamma-ray units that are designed for short source-skin distances or short diaphragm- or cone-skin distances. This applies especially to units with cone ends closed with low atomic number material such as lucite. Severe reactions will occur even if cone ends are open unless appropriate electron filters are used.[31]

## CONCLUSIONS

Supervoltage gamma and roentgen-ray radiations exert a skin sparing effect which is dependent, however, on a variety of factors. The most important are: (1) minimal electron contamination of the beam; (2) absence of bolus material overlying the skin; (3) total skin or subcutaneous doses not exceeding the tolerance of these tissues; (4) clinically acceptable time-dose intervals; and (5) favorable anatomic site.

If these optimal conditions prevail, all factors being equal, supervoltage radiation induces considerably less skin reactions, roentgen for roentgen, than conventional kilovoltage roentgen rays.

Despite the skin sparing advantages of supervoltage radiations, observable skin reactions are induced in about one quarter of all patients who undergo therapy for deep-seated malignancies and in whom parallel opposing fields are used. Approximately 10 per cent of these patients (less than 2.0 per cent of the total number treated) demonstrate significant degrees of early erythema, tanning, tanning and desquamation, and moist desquamation, especially in intertriginous zones. Subcutaneous fibrosis occurs in 5 per cent of all patients reacting (1 per cent of the total number treated).

Severe moist reactions occurring in the vulval-perineal area are not confined to

stationary therapy alone but also occur with horizontal rotational therapy.

In supervoltage therapy, skin reactions are less dependent upon field size for the same delivered dose than in 200 kv. therapy. It is not unusual in supervoltage therapy for large skin areas treated with higher total doses to react less than smaller fields to which lower total doses have been administered. Anatomic site, more often than not, determines the degree of skin reaction rather than the field area or total dose.

Supervoltage radiation induced reactions differ from those seen with conventional or lower voltage therapy in that the classic sequence of changes[3] is not always manifest; *i.e.*, erythema may or may not appear first, if at all. More often, erythema and tanning occur simultaneously, thus making it impossible to distinguish at the onset between the two; tanning or moist desquamation is frequently seen as the initial reaction.

Subcutaneous fibrosis is peculiar to supervoltage therapy and, if it occurs, it almost always follows abdominal or pelvic irradiation. This happens more frequently in obese patients but occasionally in thin patients (Case E.D., Table II). It rarely occurs if the total maximum subcutaneous dose is less than 5,000 r (Case R.B., Table II).

## SUMMARY

1. Supervoltage irradiation is skin sparing if certain conditions are met. Not all high energy gamma ray units conform to supervoltage design and may be better designated as the orthovoltage type, which can induce skin reactions similar to those in 200 kv. therapy.

2. Significant skin and subcutaneous reactions are induced by supervoltage irradiation even if optimal conditions prevail, the anatomic skin site perhaps being the most important factor, other things being equal.

3. Supervoltage radiation induced skin reactions may not follow the sequence of events described for lower voltage radiation. Erythema frequently does not occur or, if present, it merges imperceptibly with a tanning reaction.

4. Measures that can be taken to limit the incidence and intensity of supervoltage induced skin reactions are derived from knowledge and manipulation of the various factors listed in Table I.

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We wish to thank Mr. Richard Nelson of the Department of Physics, Treatment Planning Section, Memorial Hospital, New York for his cooperation in carrying out (in 1956) the surface dose rate measurements on both the 1,000 kv. machine and the theratron cobalt unit (SSD-75 cm.) recorded in Table IV.

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# ABDOMINAL IRRADIATION AND THE THYMUS OF THE ADULT RAT: THE RELATIVE IMPORTANCE OF THE ADRENAL GLANDS AND OF SCATTERED RADIATION*

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IT IS a matter of fundamental importance to determine how much of the effects of irradiating the animal are due to direct cellular damage and how much to the liberation into the blood stream of physiologically or pharmacologically active substances. The most direct way of proving the existence of such substances would be to demonstrate radiation effects in unirradiated tissues, either by cross circulation experiments or by localized, part body irradiation with adequate biologic controls for the unavoidable effects of scatter on the shielded tissues.

Cross circulation experiments in the cat failed to reveal any such "indirect" effect of radiation on hematopoiesis.[8] However, experiments in which the thymus, spleen and lymph nodes were examined after abdominal irradiation of intact and adrenalectomized rats were interpreted as showing that indirect effects of irradiation do occur, at any rate after large doses, and are mediated via the adrenal gland.[9,12] These important conclusions have been generally accepted and often quoted, even though there appears to be a hidden discrepancy in the original reports.

Leblond and Segal,[9] in 1942, published the combined results of two series of experiments, the first having been reported earlier.[12] By analyzing the two reports, it should be possible to deduce the results of their second series of experiments and this has been done in Table 1. It can be seen that there is an important difference between the results of the first and second series. In the first series, adrenalectomy indeed abolished the effect of abdominal irradiation on the weight of the thymus but, in the second series, adrenalectomy seemed to make very much less difference; in the adrenalectomized rats, the weight of the thymus was reduced by 60 per cent compared to 72 per cent in the intact rats.

It would appear, therefore, that the role of the adrenal glands in the effect on the thymus gland of local abdominal irradiation needs re-examination, especially as the general question of the degree to which the adrenal glands participate in the reactions of the body after experimental whole body irradiation is a matter of lively controversy.[1,2,5,11]

In the present experiments, large volumes of tissue were irradiated, in order to maximize the chance of observing abscopal effects in the thymus. In order to determine that changes in thymic weight were actually due to changes in cell population and did not merely reflect changes in the fluid content of the thymus, measurements were made of the total deoxyribonucleic acid (DNA) content of the thymus as well as of its fresh weight. The thymus was examined at 48 hours after irradiation, the same time interval as in the work of Leblond and Segal. Our results at this time suggest that almost the whole of the effect of abdominal irradiation on the thymus is due to the scattered radiation which affects the thymus directly; it was not possible to confirm the existence of an appreciable indirect or abscopal effect in animals with or without adrenal glands. At times later than 48 hours and after a smaller dose of abdominal irradiation, an abscopal effect on the thymus can be demonstrated, but this

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is due primarily to a decrease in the intake of food and not to any specific, radiation-induced increase in adrenal activity.[7]

## METHOD

Male albino rats of the laboratory's inbred stock were used when they were 45–66 days old and from 160–250 gm. in weight. In each experiment there were 4 litter mates which had been housed together since weaning. The animals were irradiated only after having been anesthetized by intraperitoneal amylobarbitone sodium (6–7 mg. per 100 gm.) and all the 4 rats from one litter were anesthetized together. In experiments involving adrenalectomy and part body irradiation, there were in each litter 2 unirradiated controls (1 adrenalectomized and 1 sham-operated) and 2 irradiated rats (1 adrenalectomized and 1 sham-operated but both given the same radiation treatment). The operated rats were given irradiation only to the caudal half or quarter of the body. In other experiments with intact animals, 1 rat was an unirradiated control and the other 3 were given 25 r, 50 r, and 100 r, respectively, either to the cephalic half of the body or to the whole body.

Operations were performed at the time when the animals were under the pre-irradiation anesthesia. The technique of adrenalectomy and of the sham-operations is recorded elsewhere.[7] There were no deaths after adrenalectomy. When each operated animal was killed and its thymus removed, it was inspected to see if adrenal tissue could be seen. No accessory adrenal glands have yet been found in our laboratory stock.

On all occasions the choice of treatment and the order of treatment was determined by drawing cards. Roentgen irradiation was given with 250 kv. peak therapy settings, each with a stepped filter, half value layer of 1.2 mm. Cu. The beam was always directed upwards.[4] Operated rats were given 2,000 r at 78 r per minute, focal skin distance 62 cm., or 5,000 r at 276 or 290 r per minute, focal skin distance 32 or 34 cm. The unoperated rats received their dose either at 5.9 r per minute, focal skin distance 152 cm., or at 276 r per minute; the results are separately recorded. The stated doses are "exposure" doses, *i.e.*, the dose measured in air at the position the center of an animal would occupy.

The anesthetized rats were laid belly down on a piece of brown paper to minimize heat losses by conduction to metal. When whole body irradiation was given, the paper was laid over a layer of cotton wool 1 cm. thick. When part body irradiation was given, the rat was placed partly on the cotton wool and partly on a triple sheet of lead, each sheet being 2 mm. thick. When only the caudal or cephalic half of the body was to be irradiated, the rat was so arranged that the junction between the cotton wool and lead lay immediately under the margin of the rib cage as determined by palpation *in situ*. When the caudal quarter of the body was to be irradiated, the junction lay midway between the margin of the rib cage and the anus.

After the radiation exposures had been made, the 4 rats of the litter were returned to their living cage for 48 hours and then killed. Most of the litters were deprived of all food for this period but drinking water was available *ad libitum*. Salt supplements were not given. The thymus glands were dissected out and weighed; and the total DNA-phosphorus was extracted and determined as described elsewhere.[7] The thymus glands of adult rats have not given as consistent results as the lymph nodes of adult rats or the thymus glands of young growing rats, for reasons which are not understood. Physiologic involution is already beginning in the thymus of male rats of the age and size used in these experiments. In one month all the 5 litters examined gave DNA-P values averaging about half the values obtained earlier and later, even though lymph node determinations (on other animals) made during the same month were within the expected normal range. Two other litters examined at other dates gave similarly low values but only

the series of 5 has been omitted from the results.

After all the biologic work had been done, measurements were made in a phantom of Mix-D wax (a tissue equivalent material) of the scattered dose which might have been expected to reach the thymus as a result of irradiation of the caudal half of the body by the method described above. Baldwin BD2 ionization chambers were used, with cylinders approximately 12 mm. deep and 9 mm. in diameter and a very small air volume about 2 mm. from one end. The measurements were made with the gas volume 8–10 mm. from the ventral surface of the phantom and the chamber in the midline and in the position of the manubrium of the sternum. In the anesthetized rats, the sternal notch was 6 cm. from the edge of the lead shield when the caudal half of the body was irradiated and 9.5 cm. away when the caudal quarter of the body was irradiated. The scattered dose in the phantom was determined when the central axis of the chamber was 5.5 cm. and 9.0 cm., respectively, from the edge of the lead. The dose rate was then 1.3 and 0.5 per cent, respectively, of the dose rate measured by the same chamber in the same position and with the same tube output but with the cranial half of the phantom irradiated instead of the caudal.

## RESULTS

In order that the results can be directly compared with those of Leblond and Segal,[9] the absolute values for thymic weight and DNA-P are given in Table II but the ratio of the value in an irradiated rat to that of its unirradiated litter mate is perhaps a more valuable index of effect (Table III). Comparisons within litters exclude a certain amount of between-litter variation and this may be especially useful in study of the thymus when its physiologic involution is beginning. Young mature rats were deliberately chosen for this work because experiments on the thymus of recently weaned rats had already failed to show any specfic adrenal response to ir-

TABLE I

THYMIC WEIGHT IN INTACT AND ADRENALECTOMIZED RATS GIVEN 1,980–3,680 r IRRADIATION TO THE ABDOMEN

| | Results of First Series[11] (males only) | | Results of First and Second Series Combined[8] (males and females) | | Results of Second Series* (females only) | |
|---|---|---|---|---|---|---|
| | Thymic Weight (mg.) | No. of Rats | Thymic Weight (mg.) | No. of Rats | Thymic Weight (mg.) | No. of Rats |
| Control Rats | | | | | | |
| Intact | 190 | 7 | 190 | 12 | 190 | 5 |
| Adrenalectomized | 183 | 4 | 208 | 6 | 258 | 2 |
| Abdominally Irradiated Rats | | | | | | |
| Intact | 59 | 7 | 57 | 10 | 52 | 3 |
| Adrenalectomized | 173 | 6 | 150 | 9 | 104 | 3 |
| | Mean Value for the Thymic Weight† | | | | | |
| Irradiated Rats | | | | | | |
| Intact | 31 | | 30 | | 28 | |
| Adrenalectomized | 94 | | 72 | | 40 | |

* Computed by analysis of the combined results of the two series.
† Given as a percentage of the mean value in controls.

TABLE II

THYMIC WEIGHT AND DNA-P AT 48 HOURS AFTER PART BODY IRRADIATION AND THE CHANGE IN BODY WEIGHT OVER THIS 48 HOUR PERIOD

| Area Irradiated | Caudal Half | Caudal Half | Caudal Half | Caudal Half | Caudal Quarter |
|---|---|---|---|---|---|
| Dose (r) | 5,000 | 5,000 | 2,000 | 2,000 | 5,000 |
| Postirradiation Regimen | Starved | Fed | Fed | Starved | Starved |
| Age at Death (da.) | 52 | 52 | 53 | 57 | 62 |
| Body Weight of Sham-operated Controls at Death (gm.) | 159 | 213 | 198 | 178 | 199 |
| | Change in Body Weight (gm.)* | | | | |
| Sham-operated Rats | | | | | |
| Control | −27 (6) | + 5 (5) | + 6 (4) | −32 (8) | −36 (3) |
| Irradiated | −25 (6) | −17 (5) | −10 (4) | −30 (8) | −31 (3) |
| Adrenalectomized Rats | | | | | |
| Control | −31 (6) | −12 (5) | − 9 (4) | −33 (8) | −34 (3) |
| Irradiated | −24 (4) | −20 (5) | −14 (4) | −28 (7) | −35 (3) |
| | Thymic Weight (mg.)* | | | | |
| Control Rats | | | | | |
| Sham-operated | 428 (6) | 515 (5) | 529 (4) | 432 (8) | 360 (3) |
| Adrenalectomized | 521 (6) | 521 (5) | 559 (4) | 502 (8) | 477 (3) |
| Irradiated Rats | | | | | |
| Sham-operated | 247 (6) | 251 (5) | 355 (4) | 306 (8) | 340 (3) |
| Adrenalectomized | 280 (4) | 313 (5) | 439 (4) | 391 (7) | 447 (3) |
| | Total Thymus DNA-P (mg.)† | | | | |
| Control Rats | | | | | |
| Sham-operated | 1.9 (44) | 1.7 (32) | 1.8 (34) | 1.3 (30) | 1.0 (27) |
| Adrenalectomized | 2.1 (40) | 1.7 (31) | 1.6 (31) | 1.5 (31) | 1.4 (29) |
| Irradiated Rats | | | | | |
| Sham-operated | 1.2 (48) | 0.9 (34) | 1.4 (37) | 1.0 (33) | 1.0 (28) |
| Adrenalectomized | 1.4 (51) | 1.0 (33) | 1.6 (35) | 1.1 (28) | 1.3 (28) |

* The numbers in parentheses give the number of rats on which each mean value is based.
† The numbers in parentheses give the concentration of DNA-P (μg./10 mg. thymus).

radiation[7] and it was conceivable that such a response might be shown by more mature animals of an age and size comparable to those used by Leblond and Segal.[9] For the same reason, male rats were used exclusively since the adrenal effect observed by these workers was found in male animals but not, apparently, in females (Table 1).

Abdominal irradiation of rats with 2,000–5,000 r leads to a reduced food intake and to a loss in body weight of 7–10 per cent even at 48 hours, before diarrhea becomes gross. Adrenalectomy alone led to the same degree of loss in body weight as 2,000 r irradiation, but the combined effects of adrenalectomy and abdominal irradiation were less than the sum of the two alone, presumably because a reduced food intake is common to both (Table II). With complete deprivation of food, the loss in body weight was slightly less in irradiated than in unirradiated animals, presumably because of the gastric retention which follows abdominal irradiation.

TABLE III

THYMIC WEIGHT AND DNA-P AT 48 HOURS AFTER PART BODY IRRADIATION SHOWN AS A PERCENTAGE OF THE VALUE IN THE UNIRRADIATED LITTER MATE (MEAN ± SE)*

| Area Irradiated | Caudal Half | Caudal Half | Caudal Half | Caudal Half | Caudal Quarter |
|---|---|---|---|---|---|
| Dose (r) | 5,000 | 5,000 | 2,000 | 2,000 | 5,000 |
| Postirradiation Regimen | Starved | Fed | Fed | Starved | Starved |
| Thymic Weight | (4) | (5) | (4) | (7) | (3) |
| Sham-operated Rats | 57 ± 4 | 50 ± 5 | 67 ± 3 | 71 ± 4 | 94 ± 5 |
| Adrenalectomized Rats | 58 ± 2 | 61 ± 8 | 79 ± 7 | 78 ± 6 | 94 ± 3 |
| Total Thymic DNA-P | (4) | (4) | (3) | (7) | (3) |
| Sham-operated Rats | 68 ± 2 | 50 ± 5 | 80 ± 14 | 72 ± 3 | 97 ± 5 |
| Adrenalectomized Rats | 72 ± 4 | 62 ± 15 | 102 ± 15 | 69 ± 5 | 90 ± 6 |

* The numbers in parentheses give the number of litter mate pairs on which the mean values are based.

In unirradiated animals starvation reduced thymic weight, and in starved animals adrenalectomy increased it (Table II); thus, adrenalectomy in fed animals produced little change because it also led to a reduction in food intake. The DNA-P content of the thymus was less affected by these measures but, in all 17 pairs of starved litter mates, it was greater in the adrenalectomized than in the sham-operated animal. The effect of starvation alone cannot be determined from the data because of the variation in DNA-P between litters.

The reduction in thymic weight and in DNA-P in starved animals given 5,000 r to the caudal half of the body was proportionately the same in adrenalectomized and in sham-operated animals (Table III) suggesting that the effect of abdominal irradiation on the thymus was not mediated via the adrenal glands. In fed animals there was a statistically nonsignificant difference in the direction expected if adrenal activity was relevant.

In the experimental arrangement which was used, the adrenal glands were near the boundary between the directly irradiated and the shielded areas of the body and it was conceivable that the radiation dose which the adrenal glands received would be enough to damage them and so prevent an adrenal reaction which otherwise would have occurred. To check this point the dose to the adrenal glands was reduced (a) by reducing the dose to the caudal half of the body to 2,000 r and (b) by giving 5,000 r to the caudal quarter of the body, thus ensuring that only distant scattered radiation could reach the adrenal glands. In neither case (Table III) was there a significant difference between sham-operated and adrenalectomized starved animals in the degree of reduction in thymic weight or DNA-P, though the effect of 5,000 r to the caudal quarter of the body was so small as to be in itself statistically nonsignificant.

Experiments with 2,000 r abdominal irradiation were also done with food available *ad libitum* and, as after 5,000 r, the effect of adrenalectomy was statistically nonsignificant. Nevertheless, it was noticeable after both the 5,000 r and 2,000 r doses that, in both thymic weight and thymic DNA-P, the differences between sham-operated and adrenalectomized rats were greater in fed than in starved animals (Table III) and that the differences in the fed animals were always in the direction expected if adrenal activity played some part in mediating the effects of abdominal irradiation. However, in view of the well-known effect of irradiation on food intake and of food intake on the thymus gland (Table II), it must be concluded that data on starved animals provide more reliable

TABLE IV

THE DIRECT EFFECT OF IRRADIATION ON THE THYMIC WEIGHT AND DNA-P OF MALE RATS 48 HOURS AFTER EXPOSURE UNDER DIFFERENT EXPERIMENTAL CONDITIONS*

| Dose Rate (r/min.) | Area Irradiated | Postirradiation Regimen | Age (da.) | Thymic Weight | | | Thymic DNA-P | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 25 r dose | 50 r dose | 100 r dose | 25 r dose | 50 r dose | 100 r dose |
| 276 | Cranial half | Starved | 45 | 89 | 73 | 40 | 75 | 71 | 48 |
| | | | 51 | 75 | 78 | 55 | 74 | 72 | 39 |
| 5.9 | Cranial half | Starved | 51 | 77 | 56 | 40 | 70 | 51 | 28 |
| | | | 57 | 80 | 72 | 37 | 84 | 45 | 38 |
| | | | 60 | 97 | 60 | 45 | — | — | — |
| 5.9 | Whole body | Starved | 54 | 75 | 68 | 52 | 70 | 66 | 36 |
| | | | 57 | 90 | 66 | 38 | 96 | 69 | 36 |
| 5.9 | Cranial half | Food *ad libitum* | 51 | 95 | 71 | 46 | 78 | 50 | 26 |
| | | | 52 | 86 | 78 | 45 | 96 | 92 | 42 |
| | | | 56 | 81 | 64 | 45 | — | — | — |

* Each value is for an individual rat expressed as the prcentage of that in its litter mate control.

evidence on adrenal activity after irradiation than data derived from litters with access to food.

After direct irradiation of the thymus, the concentration of DNA-P was slightly decreased, as would be expected, but, after irradiation of the caudal half of the body with a dose sufficiently large to affect the thymus, the DNA-P concentration was increased in 7 of the 8 groups (Table II). This interesting qualitative difference may be evidence for the existence of tissue dehydration following abdominal irradiation at a time before there is overt diarrhea.

*The Assessment of Scatter.* One obvious factor to consider when examining the effect of abdominal irradiation on the thymus is the direct radiation damage due to scattered radiation. Before any physical measurements of scatter were made, animals were given small doses of radiation directly to the chest in order to provide a biologic calibration curve from which could be derived the direct dose required to produce the amount of damage actually measured after the different doses of abdominal irradiation. It was realized that the actual dose rate at the thymus due to scatter from abdominal irradiation would be a certain percentage of the direct dose rate, so two sets of experiments were made, at 276 r per minute and at 5.9 r per minute, a dose rate of about 2 per cent of the 276–290 r per minute used for the 5,000 r abdominal dose. The data are given in Table IV and it can be seen that, if there were differences in effect between the two dose rates, between fed or starved animals, or between whole body or part body irradiation, the differences were quantitatively small. The pooled results may, therefore, be used legitimately as a calibration curve for the data in Table III on starved and sham-operated animals.

It can be seen that the effect on the thymus of 2,000 r or 5,000 r to the caudal half of the body could be accounted for by scatter if the dose at the thymus due to scatter was between 1.0 and 2.5 per cent of the abdominal dose. At both doses the estimate from change in DNA-P was close to the estimate from change in thymic weight, averaging 1.2 per cent for the dose of 5,000 r and 2.1 per cent for the dose of 2,000 r. After this deduction was made, direct measurement in a 200 gm. rat phantom, irradiated in the standard experimental manner, showed that the physically

scattered dose at the thymus was, in fact, of the order of just over 1 per cent. Similarly, the dose at the thymus from 5,000 r to the caudal quarter of the body must have been rather less than 0.5 per cent, judging from the biologic calibration curve, and was measured physically as 0.5 per cent. For a variety of reasons, the physical measurements of scatter are inevitably only an approximate measurement of the dose due to scatter which is actually received by the thymus gland *in vivo*[6] and the agreement between the biologic and physical dosimetry is probably really quite good.

## DISCUSSION

The results reported here differ in two ways from those reported by Leblond and Segal:[9] (a) the degree of reduction in thymic weight following a given dose of abdominal irradiation to sham-operated animals was considerably less than in their work, even though a larger fraction of the body was irradiated; and (b) the effect of adrenalectomy was very much less than in the combined results reported by them, although it was quite similar to their second series as shown in Table 1 of this paper.

There are several differences in the experimental details which may have a bearing on the differences in the results. Their adrenalectomized and sham-operated irradiated rats were matched pairs, although their unirradiated controls were not matched with the irradiated animals, whereas our animals were always litter mates. Their animals were irradiated unanesthetized and tied down to a board; our animals were always unconscious. Their animals were adrenalectomized 2–5 days before irradiation and were quite sick at autopsy 48 hours later; in fact, it is stated that some died shortly before this time. (It is also stated that some animals were killed at 66 hours, although the results on all the animals appear to have been combined together.) Our animals were adrenalectomized immediately before irradiation; none died or were moribund at 48 hours, the time when all were killed. In both cases the ventral surface of the rats faced the roentgen-ray tube and the duration of the radiation exposures was similar. The rat stocks must have differed, since the thymic weight of Leblond and Segal's controls was about half that of our controls.

It might be thought that anesthesia would produce sufficient anoxia to modify radiation responses *in vivo*. However, barbiturate anesthesia, as used here, did not appear to modify the response of the thymus in young rapidly growing rats to direct irradiation.[7] On the other hand, tying a conscious animal to a board might possibly be a strong stress stimulus which would affect the thymus in sham-operated animals with intact adrenal glands but not in adrenalectomized animals. If so, the results of Leblond and Segal[9] could perhaps have been explained away as illustrating the phenomenon of stress, with irradiation as a minor factor in the total situation. However, such an explanation cannot account for the results in Leblond and Segal's second series, as illustrated in Table 1, where the effect of the irradiation procedure in adrenalectomized animals was so substantial. The remaining factor, the variation in the length of time elapsing between adrenalectomy and examination, is of unknown significance, and it must be concluded that no wholly valid explanation is available at present of our failure to confirm the findings of Leblond and Segal. Our results did show that control of food intake is a necessary part of experiments designed to investigate adrenal activity after irradiation, and in other work reported elsewhere[7] a change in food intake after 500 r abdominal irradiation was found to be a complete explanation of the changes in the thymus occurring 3–5 days after exposure.

The results recorded in Table III seem to show that the effect of abdominal irradiation on the thymus depended scarcely at all on adrenal activity. On the other hand, the degree of effect was just that expected from the scattered radiation which must inevitably be absorbed within the cells of the thymus gland whenever the abdomen

is irradiated. Using a localized abdominal dose of 3,564 rep of deuterons (RBE = 1), Bond *et al.*[3] failed to detect any appreciable change in thymic weight until more than three days after irradiation and they concluded that "with a high energy deuteron beam lateral scatter from its path in tissue is negligible.

It is, on the whole, a little surprising to find so little evidence of adrenal activity at 48 hours after large doses of abdominal irradiation. In rats intestinal damage following lethal exposures leads to marked changes in the water and salt content of the body, which are grossly obvious by 72 hours. The equivocal evidence obtained in the present experiments that adrenal activity might be a minor factor at 48 hours is perhaps consistent with increased adrenal activity at 72 hours.

The changes in the weights of organs provide a simple means of following the evolution of radiation damage but changes in organ weight may not always reflect proportionate changes in cell populations. In the thymus of the adult rat, DNA synthesis is normally small and, unless the rate of DNA synthesis within an organ can vary quite considerably, there is little error in taking DNA measurements as a more accurate reflection of cell population than change in organ weight. As against this, measurements of DNA may be less precise than simple measurements of weight (Table IV) but, on the whole, they are not much less accurate, judging by the results reported here. With direct irradiation there is a decrease in DNA concentration; consequently, the DNA content of the thymus is a slightly more sensitive index of radiation effect than the weight of the organ.

## SUMMARY

1. The degree of damage to the thymus caused by direct irradiation with 25–100 r was not altered by a fifty fold change in dose rate.

2. It was not possible to confirm the often-cited finding that the effect of abdominal irradiation on the thymus is due to stimulation of the adrenal gland. Abdominal irradiation of starved adult rats with 2,000 or 5,000 r caused a 25–40 per cent reduction in thymic DNA-P and in thymic weight 48 hours later. However, adrenalectomy scarcely modified the degree of change which could be almost wholly accounted for by the scattered radiation which is presumed to reach the thymus. Physical and biologic measurements of the scattered dose were in agreement.

3. In control animals, adrenalectomy led to an increase in the weight of the thymus, starvation to a decrease. In view of the effect of abdominal irradiation on food intake and the effect of food intake on the thymus, evidence from starved animals is considered to be more reliable than evidence from animals with free access to food when investigating the possible existence of abscopal effects of abdominal irradiation on the thymus.

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# EFFECTS OF COMBINED ROENTGEN IRRADIATION AND CHEMOTHERAPY ON TRANSPLANTED TUMORS IN MICE*

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COMBINATIONS of irradiation and chemotherapeutic agents have been employed in treating tumors in animals as well as in man in the hope of improving the therapeutic effect. The voluminous literature on this subject has been reviewed by Bane *et al.*[2]

Heidelberger *et al.*[5] studied the effect of a single dose of 1,500 r to 2,000 r of roentgen rays alone and in combination with 5-fluorouracil (5-FU) 20 mg./kg. for 7 days on the 755 mammary adenocarcinoma and the sarcoma 180 in mice. They reported complete disappearance of all tumors after 28 to 31 days of observation. Both tumors continued to grow with 5-FU treatment alone, while the roentgen-ray treatments arrested the growth of the sarcoma and inhibited the mammary adenocarcinoma but did not cause complete regression.

Hall *et al.*[4] observed promising initial responses in squamous cell carcinomas of the lung and the head and neck as well as in certain isolated tumors of other origin, but no long term effects were mentioned.

The purpose of this paper is to report on the enhanced effect of multiple exposures of local roentgen irradiation given in conjunction with the antimetabolite 5-fluorouracil,* the antibiotic actinomycin $P_2$* ($P_2$) and the alkylating agent Cytoxan* on transplanted sarcoma 180 in Swiss Webster albino and mammary adenocarcinoma in Z inbred mice.

* 5-fluorouracil was supplied by Hoffmann-LaRoche, Inc.; actinomycin $P_2$ by Chas. Pfizer and Co., Inc.; and Cytoxan by Mead Johnson & Company.

## MATERIAL AND METHODS

### TRANSPLANTATION OF TUMORS

Female Swiss Webster albino mice weighing 25 to 30 gm. (9 to 11 weeks of age) from Taconic Farms, Germantown, New York, were used for maintaining the sarcoma 180 originally obtained from the Wisconsin Alumni Research Foundation through the McArdle Memorial Laboratory.

Male Z (Bittner C3H) mice weighing 20 to 25 gm. (6 to 10 weeks of age) bred by sister to brother matings in our laboratories were used for transplanting the mammary adenocarcinoma which originated spontaneously in one of the older female mice. While the sarcoma 180 had been transferred over innumerable generations in different hosts, the adenocarcinoma in Z mice had been transferred only twice by serial transplantation in young Z male mice.

The transplantation was performed by injecting a 10 per cent suspension of fresh wet tumor tissue pulp from the tissue press in sterile physiologic saline. A volume of 0.05 ml. was injected subcutaneously into the ventral aspect of the right hind leg. The tumor growth was relatively uniform with close to 100 per cent takes with both tumors. The sarcoma 180 produced palpable tumor nodules 4 to 5 days after transplantation and the average survival in the untreated groups varied between 15.4 and 27.3 days.

The adenocarcinoma had a slower growth rate and produced palpable tumor nodules

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after a latent period of about 2 to 3 weeks. The tumors in nontreated control mice always grew progressively until they became huge, ulcerated, and infected; the animals died usually within 10 weeks. The mice were kept at a room temperature of 75 to 80° F. under standard laboratory conditions in suspended wire-bottom cages, and fed Purina fox chow and tap water *ad libitum*. They were examined at weekly intervals, weighed and the tumors measured with calipers.

### IRRADIATION

The x-ray treatments were started 4 or 5 days after transplantation of the sarcoma 180, and after 2 to 3 weeks in the case of the adenocarcinoma, and only after a definite tumor nodule could be palpated and measured. The treatments were given with a superficial x-ray machine operated at 140 kv. peak with 1 mm. aluminum filter at 15 cm. focal skin distance, and a dose rate of $232 \pm 10$ per cent r/min., as determined with Victoreen thimble ionization chambers inserted at the position of the tumors. The half value layer was 4 mm. of aluminum. The treatments were given locally to the right leg with the tumor transplant secured in the radiation field by small battery clamps attached to the feet, while the rest of the body was outside a lead cylinder mounted on the x-ray machine tube housing.[6] This set-up ensured constant geometric relationships between the tumors and the radiation beam. In spite of a rather pronounced anode effect at this short distance, a uniform dose was given by randomization of the animals in the radiation device. No anesthetic was administered and the mice were under little stress while being irradiated. Ten mice were irradiated simultaneously.

The radiation treatments were kept uniform in all experiments, using a daily dose of 300 r for 5 consecutive days per week until a total of 17 treatments had been given or a total accumulated dose of 5,100 r over a period of 23 days. In one experiment a lower dose was used, 250 r on alternate days for a total dose of 3,000 r. The rationale for employing the above dosage schedules was to approximate those frequently used in patients.

### CHEMOTHERAPY

Preliminary toxicity studies were carried out on tumor bearing and normal mice with each of the compounds to determine the maximal dose that could be tolerated. The 5-fluorouracil was injected intraperitoneally while actinomycin $P_2$ and Cytoxan were given intravenously in volumes of about 0.2 ml. The 5-fluorouracil was dissolved in sterile physiologic saline, the actinomycin $P_2$ in a 5 per cent (V/V) aqueous acetone solution and the Cytoxan in sterile double distilled water. The largest dose which did not result in any death among a large number of mice was chosen for the combined therapy and was as follows:

*5-fluorouracil:*

(1) *Swiss albino mice:*
35 mg./kg. animal body weight daily for 5 days or the same dose for 4 days followed by 17.5 mg./kg. on the fifth day and then twice weekly for 2 weeks (Table 1).

(2) *Z mice:*
30 or 35 mg./kg. animal body wieght daily for 5 days (Table 11).

*Actinomycin $P_2$:*

*Swiss albino mice:*
1.4 mg./kg. animal body weight for 5 days or the same dose for 4 days followed by 0.7 mg./kg. on the fifth day and then twice weekly for 2 weeks, or 1.0 mg./kg. for 3 days followed by 0.5 mg./kg. on the fourth day and then twice weekly for 2 weeks (Table 1).

*Cytoxan:*

*Swiss albino mice:*
25 to 36 mg./kg. animal body weight for 3 days followed by 12.5 to 18 mg./kg. on the fourth day and then twice weekly for 2 weeks (Table 1).

The injections of the chemicals were started in the case of the sarcoma 180, 8 days and with the mammary adenocarcinoma, 2 to 3

TABLE I

SURVIVAL OF MICE BEARING SARCOMA 180

| Treatment | No. of Mice | Chemical Dose (mg./kg.) | X-ray Dose (r in 23 days) | Average Survival (days ± S.E.) | No. with Complete Regression |
|---|---|---|---|---|---|
| Controls | 9 | 0 | 0 | 25.6±4.5 | 0 |
| 5-FU and x-rays | 9 | 35 ×4<br>17.5×6 | 5,100 | 73.9±4.1[1] | 6 |
| Actinomycin $P_2$ and x-rays | 9 | 1 ×3<br>0.5×6 | 5,100 | 62.1±3.9[1] | 4 |
| Controls | 10 | 0 | 0 | 18.8±3.3 | 0 |
| 5-FU alone | 10 | 35 ×5 | 0 | 24.5±3.4[2] | 0 |
| 5-FU and x-rays | 10 | 35 ×4<br>17.5×5 | 5,100 | 62.8±7.2[3] | 2 |
| Actinomycin $P_2$ and x-rays | 10 | 1.4×4<br>0.7×5 | 5,100 | 49.2±9.0[3] | 2 |
| Controls | 9 | 0 | 0 | 15.4± 1.1 | 0 |
| Actinomycin $P_2$ alone | 9 | 1.4×5 | 0 | 14.9± 1.1 | 0 |
| X-rays alone | 9 | 0 | 5,100 | 38.6± 5.3[4] | 0 |
| Actinomycin $P_2$ and x-rays | 10 | 1.4×5 | 5,100 | 63.4±12.3[4] | 4 |
| Controls | 10 | 0 | 0 | 27.3±3.9 | 0 |
| X-rays alone | 10 | 0 | 5,100 | 56.9±5.3[5] | 3 |
| Cytoxan alone | 10 | 33 ×3<br>16.5×7 | 0 | 29.9±6.1 | 0 |
| Cytoxan alone | 10 | 36 ×3<br>18 ×7 | 0 | 31.5±5.9 | 1 |
| Cytoxan and x-rays | 10 | 33 ×3<br>16.5×7 | 5,100 | 61.6±7.4[5] | 4 |
| Cytoxan and x-rays | 10 | 36 ×3<br>18 ×7 | 5,100 | 50.8±5.0 | 1 |
| Control | 9 | 0 | 0 | 21.0±4.1 | 0 |
| X-rays alone | 9 | 0 | 5,100 | 39.8±4.7[6] | 1 |
| Cytoxan alone | 9 | 25 ×3<br>12.5×7 | 0 | 22.7±4.7 | 0 |
| Cytoxan alone | 9 | 30 ×3<br>15 ×7 | 0 | 21.2±4.2 | 0 |
| Cytoxan and x-rays | 9 | 25 ×3<br>12.5×7 | 5,100 | 34.8±6.1 | 0 |
| Cytoxan and x-rays | 9 | 30 ×3<br>15 ×7 | 5,100 | 49.8±2.7[6] | 1 |
| 5-FU and x-rays | 9 | 35 ×4<br>17.5×6 | 5,100 | 40.6±6.0 | 3 |

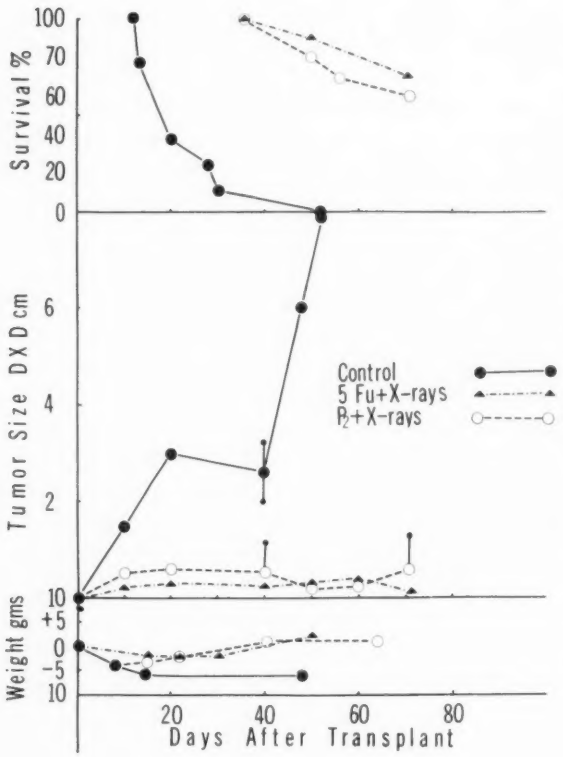
[1] Significance of difference: 5-FU and x-rays versus actinomycin $P_2$ and x-rays P=0.05.
[2] Significance of difference: controls versus 5-FU alone P=0.25.
[3] Significance of difference: 5-FU and x-rays versus actinomycin $P_2$ and x-rays P=0.25.
[4] Significance of difference: x-rays alone versus actinomycin $P_2$ and x-rays P=0.08.
[5] No significant difference between x-rays alone and Cytoxan and x-rays.
[6] Significance of difference: x-rays alone versus Cytoxan and x-rays P=0.09.

TABLE II

SURVIVAL OF MICE BEARING MAMMARY ADENOCARCINOMA

| Treatment | No. of Mice | Chemical Dose (mg./kg.) | X-ray Dose (r) | Average Survival (days ± S.E.) | No. with Complete Regression |
|---|---|---|---|---|---|
| Controls | 4 | 0 | 0 | 42.3 ± 5.8 | 0 |
| 5-FU alone | 5 | 35×5 | 0 | 41.6 ± 12.4 | 0 |
| X-rays alone | 5 | 0 | 3,000 in 28 days | 62.0 ± 5.6 | 0 |
| X-rays and 5-FU | 4 | 35×5 | 3,000 in 28 days | 62.0 ± 9.0 | 0 |
| Controls | 7 | 0 | 0 | 49.4 ± 4.3 | 0 |
| 5-FU alone | 7 | 30×5 | 0 | 48.9 ± 5.5 | 0 |
| X-rays alone | 7 | 0 | 5,100 in 23 days | 74.1 ± 2.7[1] | 0 |
| 5-FU and x-rays | 7 | 30×5 | 5,100 in 23 days | 79.1 ± 9.1[1] | 0 |
| Controls | 12 | 0 | 0 | 31.0 ± 1.3 | 0 |
| 5-FU alone | 12 | 30×5 | 0 | 42.0 ± 2.5 | 0 |
| X-rays alone | 12 | 0 | 5,100 in 23 days | 53.3 ± 3.4[2] | 0 |
| 5-FU and x-rays | 12 | 30×5 | 5,100 in 23 days | 72.8 ± 2.6[2] | 1 |
| Controls | 10 | 0 | 0 | 43.5 ± 1.2 | 0 |
| X-rays alone | 10 | 0 | 5,100 in 23 days | 53.8 ± 2.6[2] | 0 |
| 5-FU and x-rays | 10 | 30×5 | 5,100 in 23 days | 71.2 ± 1.8[2] | 0 |

[1] No significant difference between x-rays alone versus 5-FU and x-rays.
[2] Significance of difference: x-rays alone versus 5-FU and x-rays P = 0.001.




weeks after the transplantation when the tumors were distinctly palpable and measurable.

## RESULTS

Each group of animals was analyzed with respect to the survival times of the tumor bearing animals expressed in terms of the average survival (Table I and II) and in terms of fraction surviving at different time intervals (Fig. 1–9). The growth rates of the tumor transplants were computed as average tumor size expressed by the products of two opposing diameters and the average body weights at different time intervals also recorded (Fig. 1–9). The number of animals exhibiting complete tumor regression are listed in Table I and II.

FIG. 1. A comparison of effects of 5-FU and x-rays with $P_2$ and x-rays on tumor size of sarcoma 180 and on survival time and weight curves of their hosts.

The results fall in two separate groups: (a) those obtained with sarcoma 180 in albino Swiss Webster mice, and (b) those obtained with mammary adenocarcinoma in inbred mice of the Z strain.

*Sarcoma 180.* In the analysis of the survival times, it was apparent that the animals which received combined 5-fluorouracil and x-ray therapy outlived all the others. The average survival times in two different experiments were 73.9 and 62.8 days, respectively, as compared with 25.6 and 18.8 days in the nonirradiated controls and 62.1 and 49.2 days in animals receiving combined actinomycin $P_2$ and x-ray treatments. The difference between combined treatments with 5-fluorouracil and x-rays and actinomycin $P_2$ and x-rays was significant in the first experiment ($P=0.05$).

In the analysis of the growth rates of the tumors, a marked inhibition was evident in the group which received combined treatments when compared with the less pronounced effect from chemotherapy or x-ray therapy alone. This was demonstrated when irradiation in combination with both 5-fluorouracil and actinomycin $P_2$ was used as shown in Figure 1, 2 and 3.

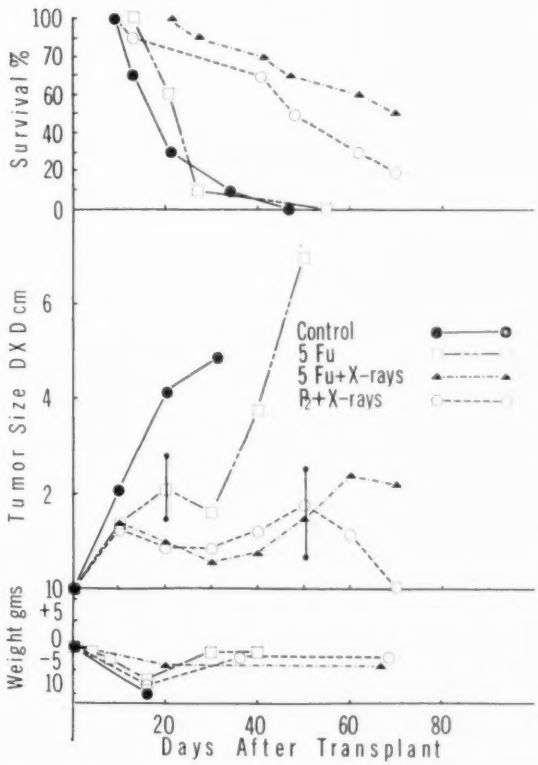



FIG. 2. A comparison of effects of 5-FU, 5-FU and x-rays, and $P_2$ and x-rays on tumor size of sarcoma 180 and on survival time and weight curves of their hosts.

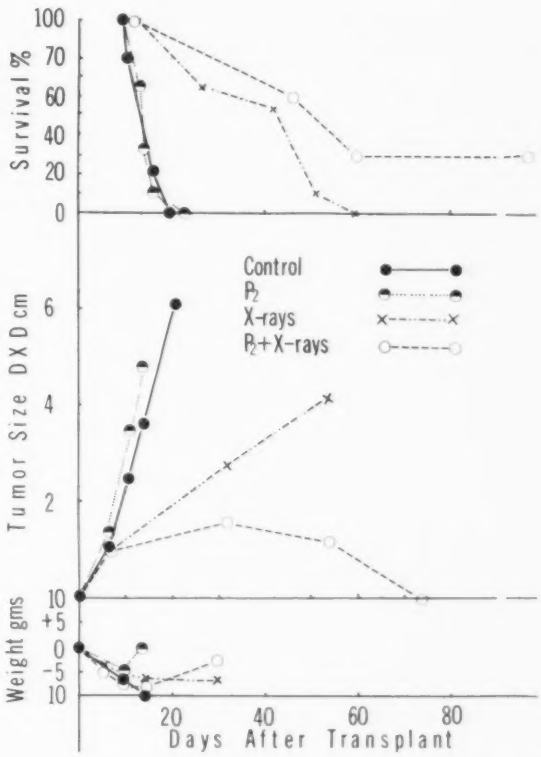



FIG. 3. A comparison of effects of $P_2$, x-rays, and $P_2$ and x-rays on tumor size of sarcoma 180 and on survival time and weight curves of their hosts.

In 8 out of 19 animals treated with 5-fluorouracil and x-rays and in 10 out of 29 treated with actinomycin $P_2$ and x-rays, complete tumor regression occurred. Irradiation alone failed to produce complete tumor regression although tumor growth was retarded; nevertheless, all animals died with growing tumors (Fig. 3). The average survival time in this group was 38.6 days, as compared with 15.4 days in the control and 63.4 days in the group receiving combined treatment with actinomycin $P_2$ and x-rays. The difference between the average

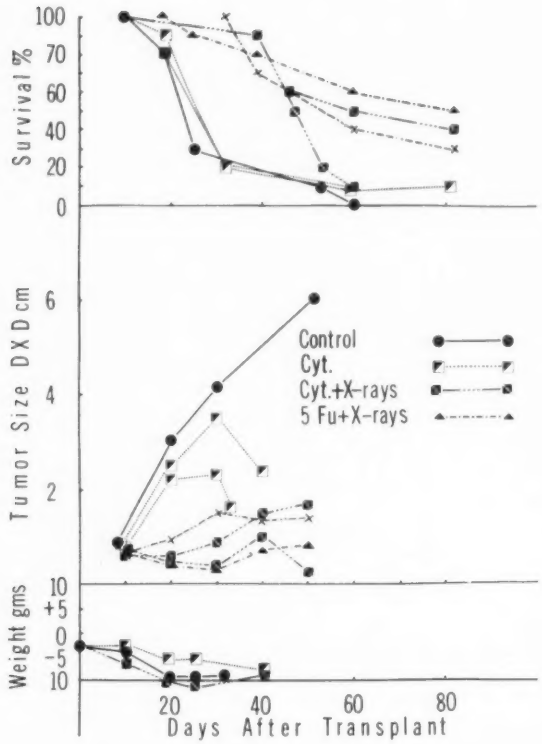



FIG. 4. A comparison of effects of Cytoxan, Cytoxan and x-rays, and 5-FU and x-rays on tumor size of sarcoma 180 and on survival time and weight curves of their hosts.

survival of animals treated with x-rays alone and those receiving combined actinomycin $P_2$ and x-ray treatment is on the borderline of statistical significance ($P = 0.08$). In this experiment the combined therapy resulted in complete tumor regression in 4 out ot 10 animals while no regression resulted from x-ray treatments alone. Similarly, 5-fluorouracil or actinomycin $P_2$ alone failed to arrest the growth of these tumors (Fig. 2 and 3).

Owing to the fact that many of the animals which received combined treatments were still alive at the time of writing, the average survival rate expressed in the tables is minimal and will obviously increase as long as these animals survive. Thus, the differences observed will become more significant, since all animals which received chemotherapy or x-ray treatments alone are dead.

In the analysis of the weight curves, it became apparent that the combined therapy resulted in no more weight loss than did the chemotherapy alone. All animals which showed complete tumor regression rapidly regained their weight. Slightly greater weight loss occurred with actinomycin $P_2$ and x-rays than with 5-fluorouracil and x-rays (Fig. 1, 2 and 3).

The two experiments with Cytoxan are still incomplete. The data obtained suggest that Cytoxan alone in the dose levels employed could not arrest the growth of the tumor nor increase the survival of the animals (Fig. 4 and 5). Cytoxan administered in conjunction with x-rays in dose levels of

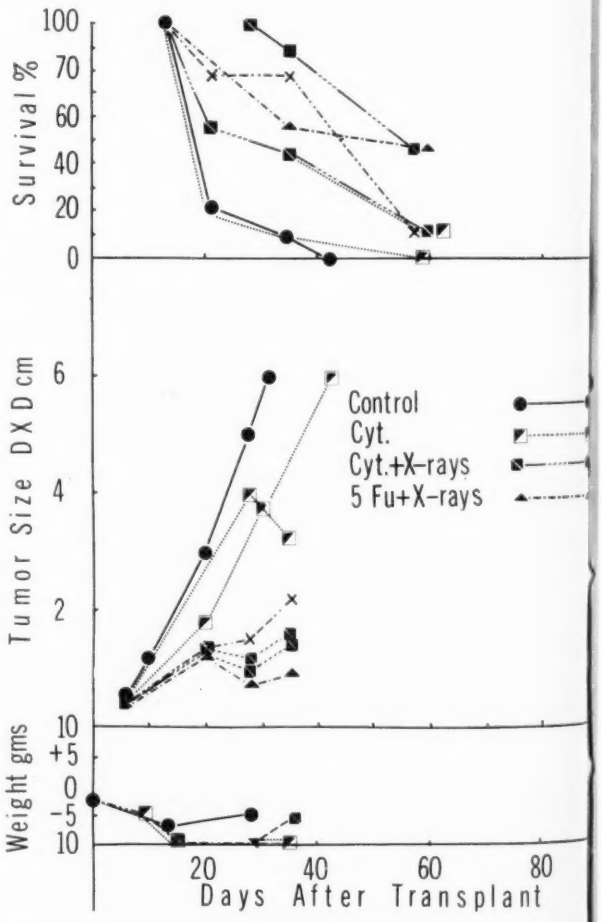



FIG. 5. A comparison of effect of Cytoxan, Cytoxan and x-rays, and 5-FU and x-rays on tumor size of sarcoma 180 and on survival time and weight curves of their hosts.

36 mg./kg. animal body weight appeared too toxic and 25 mg./kg. had no increased effect on the tumor as compared with x-rays alone. Cytoxan administered in combination with x-rays in dose levels of 30 or 33 mg./kg. proved quite effective, however, and caused complete tumor regression in 4 out of 10 animals in one experiment and in 1 out of 9 in the other. Our data suggested the importance of choosing the optimal dose of the chemical for achieving enhanced radiation effects on the tumors (Table 1).

The average survival so far compares favorably with that obtained with combined 5-fluorouracil and x-ray treatments in these experiments. Irradiation alone produced complete tumor regression in 3 out of 10 animals of the first and in 1 out of 9 animals of the second experiment, emphasizing that further studies are needed before definite conclusions can be drawn regarding enhancement of radiation effects on the tumors by Cytoxan.

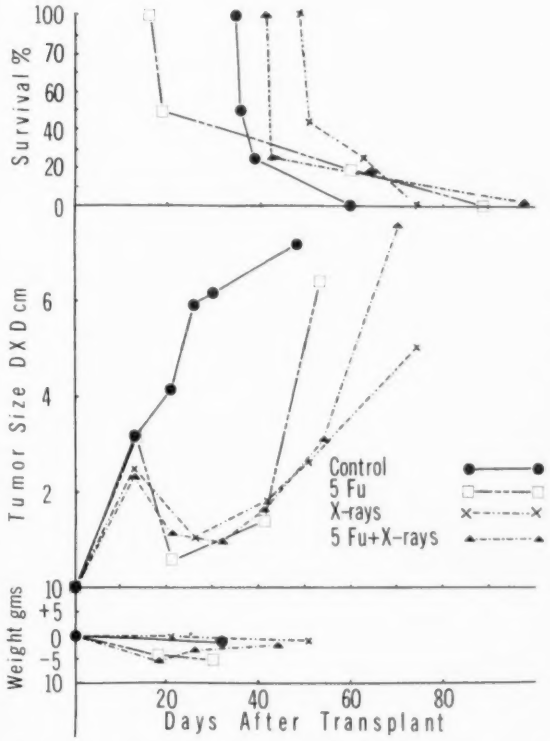



Fig. 6. A comparison of effects of 5-FU, x-rays, and 5-FU and x-rays on tumor size of mammary adenocarcinoma and on survival time and weight curves of their hosts.

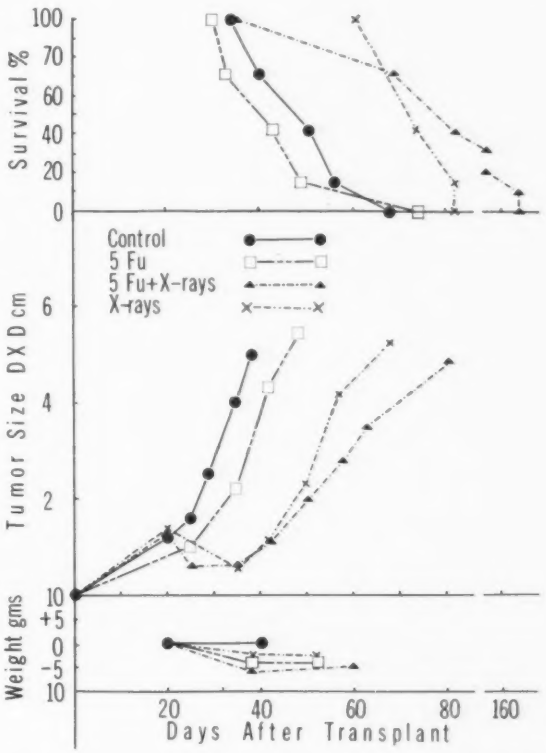



Fig. 7. A comparison of effects of 5-FU, 5-FU and x-rays, and x-rays on tumor size of mammary adenocarcinoma and on survival time and weight curves of their hosts.

*Mammary Adenocarcinoma in Z Mice.* Experiment No. 1 (Table II) represented a preliminary study with small groups of animals. The doses of 5-fluorouracil and x-rays proved unsatisfactory. These were subsequently changed as the dose of 5-FU proved too toxic and the x-ray dose inadequate. In the second experiment with 7 animals per group, the combination of x-rays and 5-FU treatments resulted in some increase in the average survival time as compared to x-ray treatments alone, but the difference was not statistically significant. All mice died with growing tumors. The weight loss was slight (Fig. 6 and 7).

In subsequent experiments larger numbers of tumor bearing animals were used. Those that received combined x-ray and 5-FU treatments showed a statistically

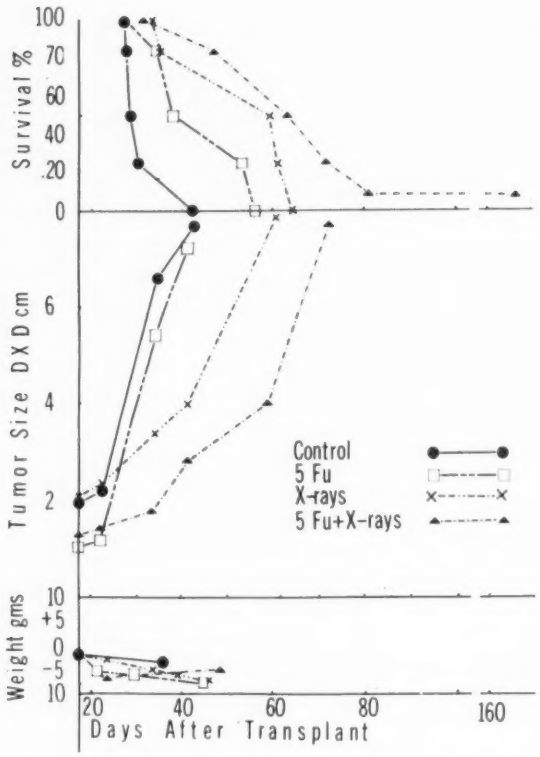



FIG. 8. A comparison of effects of 5-FU, x-rays, and 5-FU and x-rays on tumor size of mammary adenocarcinoma and on survival time and weight curves of their hosts.

significant increase in the average survival time when compared with mice treated with x-rays alone (72.8 and 71.2 days as compared with 42 and 53.8 days, with P = .001 in both experiments). All animals died, however, from progressive tumor growth with 1 exception. In this single mouse the tumor regressed completely and the animal is still alive, 150 days after the transplantation. The slight loss in animal body weight suggested a minimum of toxicity (Fig. 8 and 9). In three experiments the growth of the tumors was more inhibited by the combined treatments than by either chemotherapy or roentgen therapy alone.

## DISCUSSION

These experiments were initiated after attempts at evaluating the possible merits of combined chemotherapy and roentgen therapy in far advanced malignancy in humans had given inconclusive results in our institution. Suitable controls in the human studies reported were noticeably absent so that an enhanced antitumor effect by the combination could not be proved unequivocally.

The ready availability of animal controls and the employment of the same tumor in all animals in terms of quantity and time of inoculation obviate the shortcomings of the human studies.

The limitations of studies of this nature in terms of applying the results to clinical work are well recognized. Such limitations are, however, inherent in any type of screening of chemical agents against animal tumors. A good example is the failure of 5-fluorouracil administered alone to produce regression of established transplanted mouse tumors even when given in near

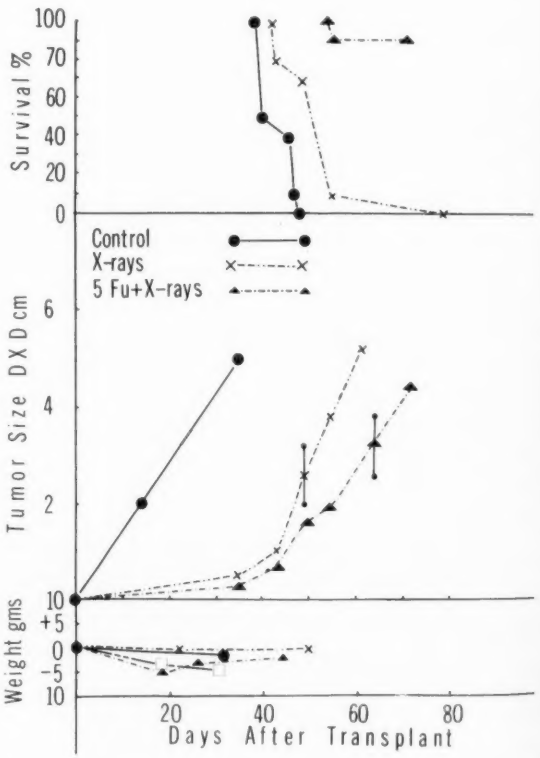



FIG. 9. A comparison of effects of x-rays, and 5-FU and x-rays on tumor size of mammary adenocarcinoma and on survival time and weight curves of their hosts.

lethal doses when it has been demonstrated repeatedly that this compound may result in dramatic regression of advanced tumors of the breast, colon and ovary in the human.[3]

Spontaneous tumors in inbred mice may be preferable for this type of work but they are not readily available in the large numbers necessary for statistical studies. Furthermore, there is no assurance that results obtained with spontaneous tumors have more validity in human tumors than those obtained with transplanted tumors. The great variety of tumors in the human precludes any generalization as to the merits of combined chemo- and roentgen therapy based on results obtained in animal experimentation.

Certain chemotherapeutic agents have shown a preferential antitumor activity against certain types of malignant neoplasms. As all three agents studied in combination with x-ray therapy showed an increased effect over x-ray therapy alone, the compound most likely to produce a response in a given tumor could be chosen for the combined treatment.

Reports from our institution had previously pointed out that irradiation to large flat bones as in the pelvis resulted in marked leukopenia when fluoropyrimidines were subsequently administered.[1] This phenomenon was also observed when Cytoxan was given subsequent to pelvic irradiation. Actinomycin $P_2$, however, did not produce leukopenia in our animal and human studies and lent itself admirably to combination treatment with irradiation.

## CONCLUSIONS

Sarcoma 180 transplanted to Swiss Webster albino mice and mammary adenocarcinoma, originating spontaneously in inbred Z ($C_3H$) mice and transplanted for two generations in the same strain, were used for studies on the effects of combined chemo- and roentgen therapy.

Treatments with 5-fluorouracil, actinomycin $P_2$ or Cytoxan and fractionated x-ray therapy resulted in increased inhibition of the growth of the tumors as well as prolonged survival of the animals when compared with either chemotherapy or x-ray therapy alone.

Further studies in an attempt to determine the optimal time dose relationship in a wider spectrum of tumors are being pursued currently at our institution.

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# *In Vivo* DOSIMETRY WITH MINIATURE GLASS RODS*

## PART I. PHYSICAL ASPECTS AND RECENT DEVELOPMENTS

*By* STANLEY J. MALSKY, CHARLES G. AMATO, CYPRIAN B. REID, CHARLES SPRECKELS *and* L. MADDALONE
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THE glass dosimeter† employed weighs approximately 830 μg., is 1 mm. in diameter and 6 mm. in over-all length. Its use is based upon the principle of radiophotoluminescence,‡ a phenomenon first described by Prizbran[18] thirty-four years ago.

### PRINCIPLE AND DESIGN

The dosimeter is comprised of a glass host consisting of barium-potassium-aluminum metaphosphate containing a deliberately added impurity, silver metaphosphate, which acts as the source of the fluorescent activator. The transmission or absorption of ionizing radiation produces many effects, only three of which are of interest in this presentation. They are: the production of photoelectrons, the dissociation of the silver metaphosphate, and the reduction of ionic silver to metallic silver. The last effect is irreversible. When ionic silver is exposed to ultraviolet light, it absorbs, transmits or reflects the ultraviolet rays. However, the metallic silver will alter the frequency and hence the wave length of the incident ultraviolet excitation. The result is the emission of an orange-yellow fluorescence, the intensity of which is directly proportional to the number of metallic silver fluorescent centers present, and hence is directly related to the cumulative radiation exposure. By the proper use of optical by-pass filters and a photomultiplier tube, the fluorescence can be converted into a direct current signal. Due to the linear relationships present, a relative dosimetry system results.

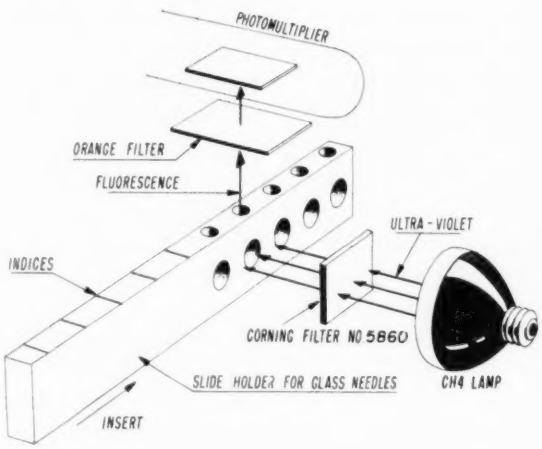


FIG. 1. The glass dosimeters are mounted perpendicular to the ultraviolet source. Fluorescence output is proportional to the amount of radiation received.

Figure 1 illustrates the method by which the fluorescence is produced and converted to an electrical signal. The needles are read in this fluorimeter, called a reader. The reader system employed in this investigation is one developed by Dr. Schulman and his associates[19,20] of the U. S. Naval Research Laboratory.

Figure 2 is a block diagram of the entire reader. The use of an isolating transformer, the autotransformer and the two monitoring voltmeters was an experimental precaution and need not be employed during routine work.

Figure 3 is a schematic diagram of a balanced bridge electrometer amplifier designed by Caldwell[4] and modified by our staff. The range selection is obtained by placing a voltage divider in the input circuit. Batteries supply filament, grid and

† Both regular composition and low Z glass are obtainable from the Bausch and Lomb Optical Co.

‡ Radiophotoluminescence is a phenomenon whereby a material, originally nonluminescent under visible or ultraviolet light, is made responsive to such light excitation by exposure to roentgen or gamma radiation.

* From the Radiophysics Research Section, Radiotherapy Service, Veterans Administration Hospital, Bronx, New York.
Presented at the Forty-second Annual Meeting of the American Radium Society, San Juan, Puerto Rico, March 17–19, 1960.

plate voltage. The value of the screen grid resistor (shown as 27,000 ohms) must be experimentally determined. The proper value permits the current in the arms of the bridge to be balanced when no input signal is applied and the zero potentiometer is in its midposition. This resistance value must be redetermined whenever any circuit parameter is altered.

The reader just described can be assembled for about $600.00. A commercially available reader is under development.* If this reader is used, its linearity and range must be critically evaluated. Any reader should exhibit a linear response and should read up to 10,000 r. A radiation detector should be energy and rate independent and should have either a linear or log response.

Numerous articles have been published in the literature relating to the physical characteristics.[5–10] We are continuing investigations into those properties displayed by the regular glass dosimeter and that of the low Z glass (containing lithium-manganese-aluminum metaphosphate).[12,13] Both types of microdosimeter glass can read up to 10,000 r (with shields), and beyond this limit by measuring the change in optical transmission. The unshielded or bare glass must be considered energy dependent whenever photon energies of less than 1 mev. are encountered.[14] To overcome this, proper shielding must be provided.[15] This was one of the goals of our work, when a minimum diameter shield was evolved so that the entire assembly would permit human *in vivo* measurements. Toxic materials were eliminated from consideration as a shield material. Minimum wall thickness requirements suggested the use of pure gold or platinum; gold was selected due to cost considerations and ease of fabrication.

Figure 4 illustrates a prototype of our final shield design. A properly designed shield must admit a percentage of the softer component of the beam. If the shield is not properly designed, the dosimeter may fail

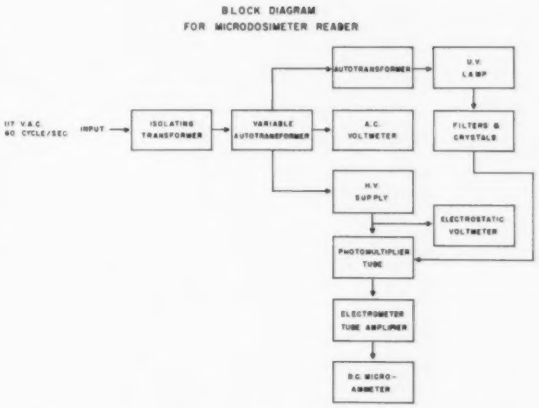


Fig. 2. Block diagram of microdosimeter reader.

to record either a major or important component of the radiation field being measured. To permit recording of lower energy gamma or roentgen rays, a series of small holes or portals was drilled into the shield wall. Number 80 drill bits were employed. Four to forty portal areas were evaluated with varying wall thicknesses and a definite correlation was found between the portal area and the surface-to-depth response.

The final design indicates that the gold wall thickness for the regular glass needle should be 17 mils while for the low Z glass

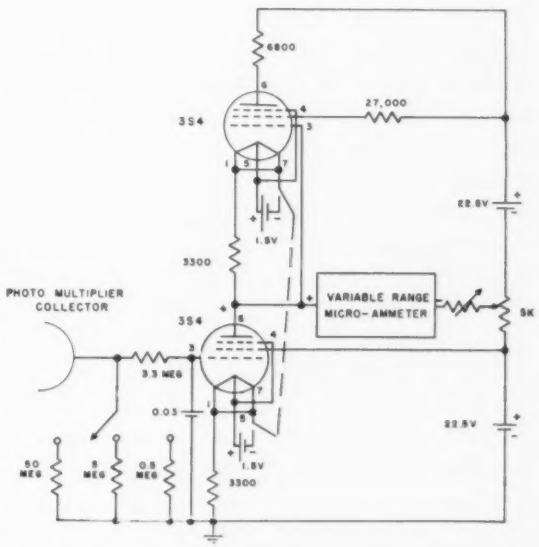


Fig. 3. Balanced bridge electrometer amplifier. Three range selector switch allows a wide range of readings.

* Literature is available from the Bausch and Lomb Optical Co.

Fig. 4. Prototype of final gold shield to correct for energy dependence in the photon energy range of 0.25 to 1.33 mev.

needle it should be 10 mils. With the proper wall thickness and open portal area, the dosimeter should then be energy independent over the photon energy range of 0.25 to 1.33 mev.

## APPLICATIONS

*Gamma ray spectroscopy.* Due to the relationship between photon energy and the mass absorption cross section for a given material, any properly and differentially shielded radiation detector may serve as a spectrometer if the techniques of absorption spectroscopy are applied. Silberstein[21,22] outlined the basic mathematical techniques required for continuous roentgen-ray spectra. Bell,[3] Jones[10] and Greening[7] have published analyses of Silberstein's method. Greenfield *et al.*[6] developed a digital computer code to obtain spectral distributions from a filtration system. A set of at least seven shields of different wall thicknesses is required. Figure 5 shows a set of filters that the authors have employed. A plot of the resulting dosimeter readings against wall thickness yields a filtration curve. Use may be made of this curve to establish an empirical relationship which should, upon proper mathematical treatment, yield the spectral distribution. Use of the glass needles would appear attractive; however, before employing them certain limitations must be noted: (1) the detector must be energy independent in the energy

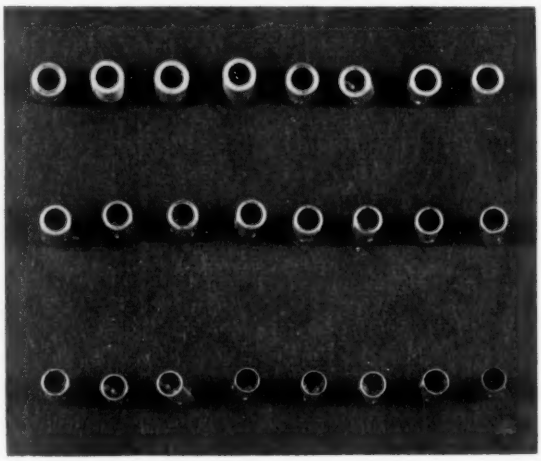

Fig. 5. A series of filters for use in absorption spectroscopy. Wall thicknesses vary from 1 mil (lower right) to 24 mils (upper left).

regions of interest, or, if it is energy dependent, this problem can be resolved by (a) suitable correction coefficients or (b) the creation of an energy independent shield; and (2) the mathematical formulation must permit analysis not only of a continuous spectrum, but also of a discrete spectrum, produced by either isotopes or neutron capture gamma rays.

*Gamma neutron determinations.* Kondo[11] established the relative neutron insensitivity of these needles. This has been confirmed in our studies. There is almost no response to fast neutrons and a response giving a reading of 1 r for every $5 \times 10^9$ NVT of thermal neutrons.[23] Workers at the Oak Ridge National Laboratory[23] believe the volume of the dosimeter justifies the cost of enriched $Li^6$ shields to eliminate thermal neutron response and permit gamma dosimetry in the presence of an intense neutron beam. One approach that might provide a more economical solution is the use of neutron shields composed of commercially available brazing material. Such alloys contain varying percentages of cadmium combined with gold and zinc or copper. While such a shield will not eliminate activation of the glass, it will reduce this to an acceptable level. The contribution of neutron capture gamma rays originating within the shield should also be insignificant. Preliminary work using bare and boron shielded dosimeters has been encouraging.

*Neutron spectrometer.* One other possible area of application is the use of the needle as a crude neutron spectrometer. Since the needle composition is known and an analysis of the decay spectrum is possible, the decay products can be identified and correlated with neutron energy. For instance, $Na^{24}$ would be produced by the n, $\alpha$ reaction with $Al^{27}$. The threshold for this reaction is slightly over 8 mev., thereby indicating the presence or absence of an energetic neutron beam component. The decay of the $Ag^{110}$ isomer could be used to measure thermal neutrons.

## SUMMARY

1. The radiophotoluminescent glass dosimeter can be employed to measure radiation within the human system and a relative calibration system can be obtained for standard techniques of calibration.

2. Although the dosimeter is energy dependent for various photon energies, this factor can be eliminated in part for a specific photon range by the use of a suitable shield.

3. The use of a low Z composition glass makes possible a reduction in the wall thickness of the gold employed in the shield material.

4. The glass dosimeter can be used *in vivo* to obtain a gamma ray spectrum with the aid of accepted techniques of absorption spectroscopy. However, machine calculations are necessary due to the mathematical analysis required.

5. The glass dosimeter can be used, with a suitable lithium shield, for the measurement of gamma rays in the presence of intense neutrons.

6. The glass is being investigated for possible use in a neutron spectrometer.

7. The bare dosimeter is being investigated for total and partial absorption of various energy beta rays.

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The authors wish to express their appreciation to Dr. Schulman and Mr. Attix of the U. S. Naval Research Laboratory, and to Mr. R. Goebel and Mr. A. Ammann for their assistance in this study.

## REFERENCES

The references are given at the end of Part II of this work.

# *IN VIVO* DOSIMETRY WITH GOLD-SHEATHED MINIATURE GLASS RODS*

## PART II. CLINICAL APPLICATIONS IN RADIATION THERAPY

*By* BERNARD ROSWIT, M.D.
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IN RADIATION treatment of deep seated human cancer, there is an outstanding need for a miniature radiation detector by which to measure dosage with accuracy and with ease in all body tissues and spaces. Particularly is this so today when high energy and nuclear sources have become widely available for more radical cancer therapy—with greater risk to critical normal structures. It is generally agreed that radiation measurements within the body are far more dependable than calculations or phantom values. With this objective we surveyed existing detector systems, such as air-cavity units, Geiger-Müller counters and scintillation crystals. We could find no single instrument which fully satisfied our criteria for an "ideal" *in vivo* dosimeter for routine clinical use (Table 1).

TABLE I

CRITERIA FOR AN "IDEAL" IN VIVO DOSIMETER

1. Miniature size (about 1×10 mm.)
2. Reasonable clinical accuracy (within ±10 per cent)
3. Wide therapeutic dose range (from 50 r to 10,000 r)
4. Freedom from electrical shock hazard (no cables)
5. Stability under rugged clinical conditions
6. Applicability in multiple units for homogeneity studies
7. Easy identification within the body and upon removal
8. Integration of repeated daily exposures (up to 10,000 r cumulative dose)
9. Independence of beam direction within the body
10. Temperature and humidity independence at reasonable levels
11. Independence of dose rate variations
12. Nontoxic to human tissues
13. Unaffected by human secretions or excretions
14. Permanent dose recording in detector, for future reference
15. Re-usable—after simple processing
16. Energy independence in the entire spectrum of therapeutic radiation now utilized for treatment of deep seated cancer
17. Correct reading in the whole range of energies most likely to be encountered within the body, regardless of portal size or depth in tissue
18. Reproducibility of response
19. Unaffected by reading procedure (no discharge of fluorescence)
20. Easy sterilization
21. Minimal cost

### I. THE UNSHIELDED RADIOPHOTOLUMINESCENT GLASS ROD

#### A. PHYSICAL CHARACTERISTICS

A tiny photoluminescent glass rod originated by Schulman and his associates[19,20] appeared to offer the most fruitful possibilities as a practical clinical dosimeter. Its physical characteristics have been described by these investigstors, by our own group,[1,2,12,14,17] and by others.[4,5,8,11] Part 1 of our study deals in detail with this development in our laboratory (see preceding article).

Briefly, the dosimeter consists of a cylindrical rod of silver-activated glass containing potassium, barium, aluminum and phosphate. It measures 1 mm. in diameter by 6 mm. in length.

Under irradiation, the positive silver ions are converted to stable silver atoms through capture of electrons ejected from the glass. When subjected to an ultraviolet light in an appropriate "reader," the silver atoms (luminescent centers) produce an orange-yellow fluorescence. A photomultiplier system in the reader converts this fluorescence into an electrical current recorded in microamperes and read as roentgens. The effect is directly propor-

* From the Department of Radiation Therapy, Veterans Administration Hospital, Bronx, New York. Presented at the Forty-second Annual Meeting of the American Radium Society, San Juan, Puerto Rico, March 17–19, 1960.

tional, in a linear fashion, to the radiation absorbed by the glass.

Standard glass rods of known exposure (fluorescence) are employed to "zero in" the reader system prior to use and serve to check the stability of the equipment during use. Inasmuch as some fluorescence occurs during manufacture, it is necessary to secure a pre-dose reading before each exposure, later to be subtracted from the gross fluorescence.

### B. ADVANTAGES

In our clinical and laboratory experience of more than three years, the glass rods appeared to offer unique advantages over more conventional dosimeters. They were of optimum size and shape and provided an accuracy of ± 1–2 per cent under experimental conditions, with variations of ± 5–10 per cent in limited clinical settings. They required no electrical cables or light-pipe systems within the body and could be freely employed in multiple units. Directional independence was noted in the body and in phantoms, but not in air. No corrections were needed for temperature and humidity changes during routine clinical exposure. Cumulative dose readings as high as 10,000 r and as low as 50 r were recorded with reproducible accuracy from rod to rod with single or cumulative exposures. The dose record was permanent (up to three years thus far) until erased by a simple heating procedure. The dose recording was unaffected by repeated exposure to the mercury lamp in the reader and was observed to be dose-rate independent.

Of the greatest interest was the absence of energy dependence in the high energy therapeutic range (1–2 mv., cobalt 60, cesium 137, iridium 192, radium and radon). While a commercial reader is presently available,* a "do-it-yourself" model can be fabricated for about six hundred dollars. The glass rods may be secured from a commercial source* at minimal cost (less than fifty cents each) and re-used after heating.

* Bausch & Lomb Optical Co., 730 Fifth Ave., New York, New York.

### C. DISADVANTAGES

We observed a striking energy dependence of the bare glass below the supervoltage range. These values are not linear and may vary by as much as ± 20 per cent from the delivered dose. We noted markedly increased sensitivity to softer, scattered radiation with portals greater than 150 cm.$^2$ and tissue depths greater than 8 cm. These are sharp limitations indeed to effective use of any dosimeter in radiation therapy practice.

Chipping, cracking and breaking of the glass results in reflection and refraction of these defects and false values. With reasonable care, however, the latter has not been a problem in our clinic. Although nontoxic to human tissues, the bare glass develops false fluorescence through contamination with body fluids and secretions. While plastic tubing can overcome this difficulty, it remains impossible to identify the position of the rods within the body because glass and plastic are both radiolucent. To compare the dosimeter reading with calculated or phantom values for tissue or tumor dose (Table II), one must obviously establish the precise geometric position of each dosimeter in the body and identify each unit when removed for reading.

After radiation exposure, reading should be delayed to permit complete readjustment of the internal glass structure in order to achieve the highest reading accuracy. For 90 per cent of the final reading one should wait two hours; four hours for 95 per cent values; and twenty-four hours for approximately 100 per cent or "true" reading.

## II. THE GOLD-SHIELDED PHOTOLUMINESCENT GLASS ROD

### A. TECHNICAL DEVELOPMENT

It appeared to us that most of the important shortcomings of the bare glass rod, particularly the problems of energy dependence, identification, contamination and damage, could be overcome by development of a filter, shield, cartridge or sheath,

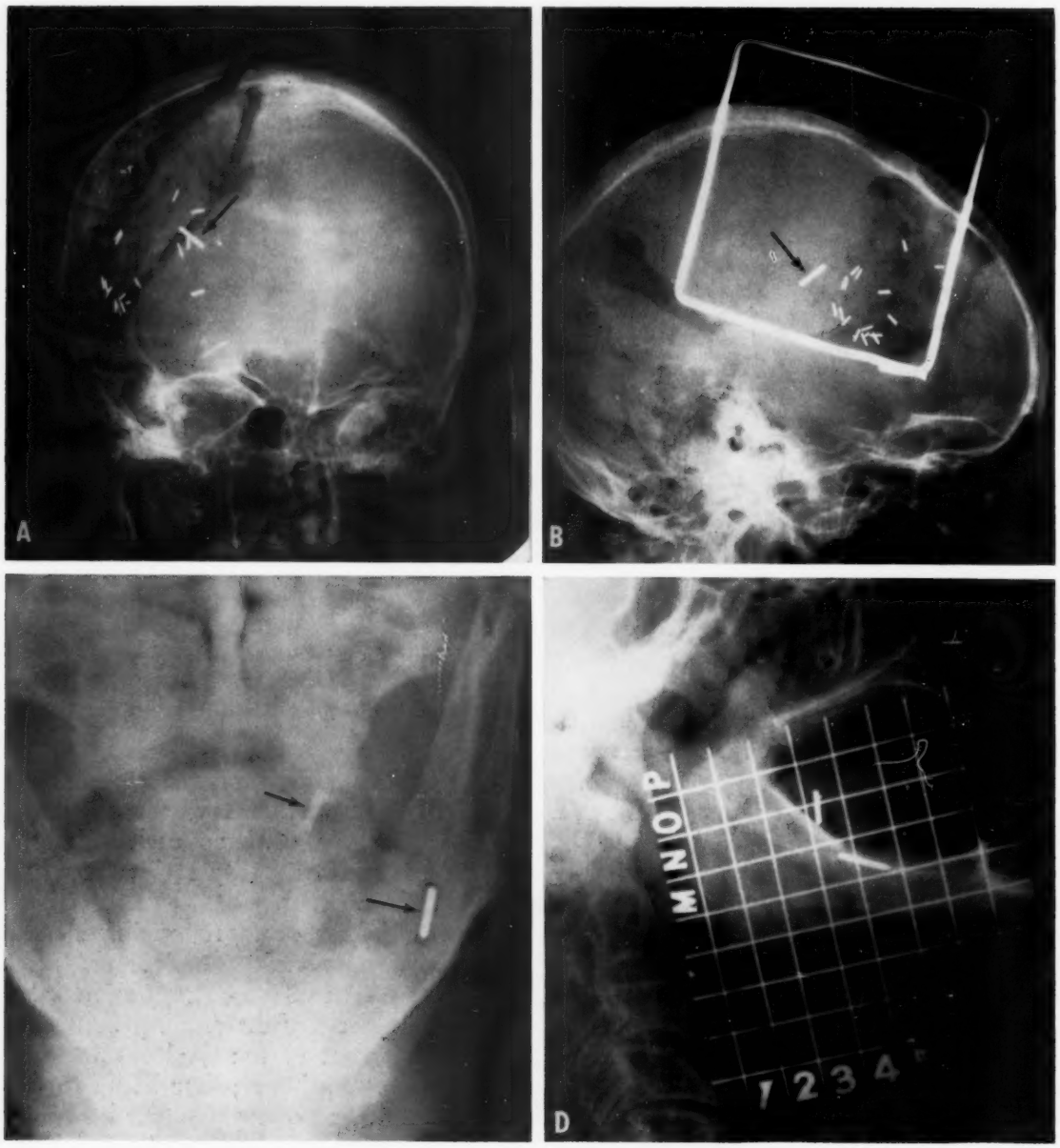



Fig. 1. (*A*) The microdosimeter is visualized here in the brain of a young man with a nonresectable glioblastoma. It was lodged in the body of the tumor in a No. 8 French polyvinyl catheter during the exploratory craniotomy (courtesy Dr. Eric Krueger). The tiny metal clips mark the several extensions of the neoplasm into contiguous normal brain tissue. (*B*) In this lateral view of the patient shown in *A*, the gold capsule carrying the dosimeter is clearly seen, oriented within a lead-solder outline of the treatment portal, ready for the first exposure. After the third exposure, the catheter with its dosimeter was withdrawn and the reading compared with a phantom value. There was an excellent correlation. (*C*) In this patient, with a massive carcinoma of the tongue, it was of interest to compare readings in the tumor and the mandible at orthovoltage (260 kv.) and at cobalt 60 energy levels. One dosimeter may be seen in the tumor and another in a drill hole in the mandible. (*D*) Lateral view of the arrangement of dosimeters shown in *C*, utilizing a metal grid to outline the portal and to orient the position of the detectors. This study is to be extended to secure ample data on absorption in bone at various energy levels. (*E*) This huge defect is the result of several futile surgical attempts to control an invasive carcinoma of the left maxillary sinus. Orthovoltage

→

TABLE II

A CROSS-SECTION OF REPRESENTATIVE CASES FOR COMPARISON OF THE RECORDED DOSIMETER VALUES AND CALCULATED OR PHANTOM DOSE

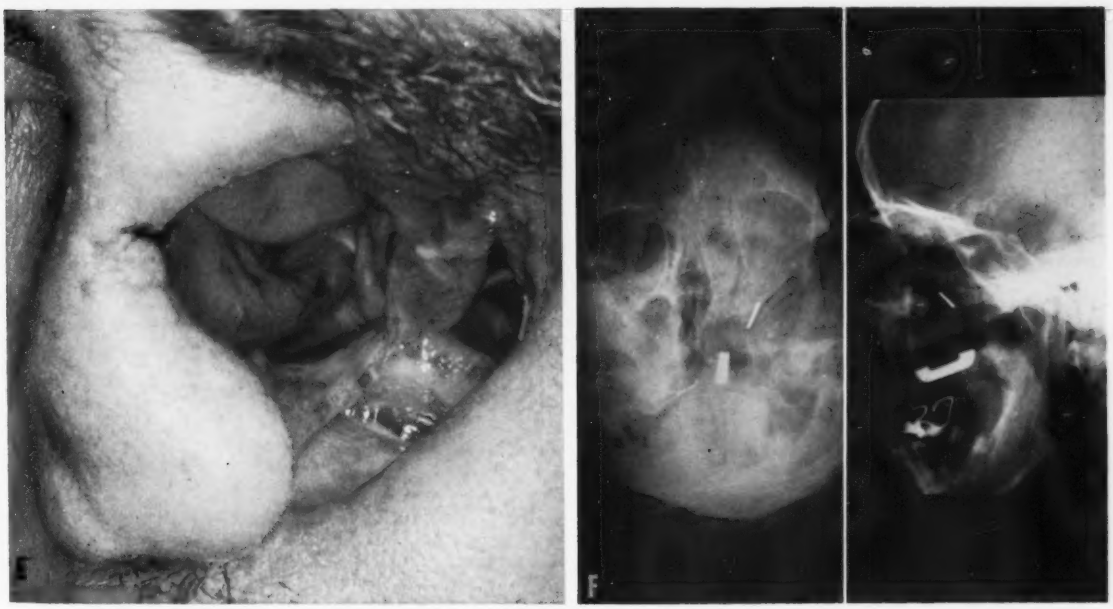
| Case No. | Site | Treatment Modality | Dosimeter Value (r) | Calculated Value (r) | Per Cent Deviation |
|---|---|---|---|---|---|
| 1. (Fig. 1, *E* and *F*) | Antrum | $Co^{60}$ | 211 | 2.1 | −4.7 |
| 2. (Fig. 2*F*) | Bladder | $Ir^{192}$ | 4,200 | 4,000 | +5.0 |
| 3. (Fig. 2*B*) | Neck | $Co^{60}$ | 286 | 273 | +4.8 |
| 4. (Fig. 2*D*) | Cervix | Ra | 990 | 960 | +3.1 |
| 5. (Fig. 2*E*) | Chest Wall | $Ir^{192}$ | 1,877 | 1,832 | +2.5 |
| 6. (Fig. 3, *A* and *B*) | Bronchus | $Co^{60}$ | 248 | 239* | +3.7 |
| 7. | Face | 260 kv. | 200 | 192 | +4.2 |
| 8. | Breast | 1 mv. | 210 | 200 | +5.0 |
| 9. | Kidney | 1 mv. | 140 | 138 | +1.5 |
| 10. | Bladder | 1 mv. | 170 | 176 | −3.4 |
| 11. | Kidney | $Co^{60}$ | 76 | 80 | −5.0 |
| 12. | Rectum | Ra | 520 | 540 | −3.7 |
| 13. | Neck | 260 kv. | 200 | 192 | +4.2 |
| 14. | Stomach | $Co^{60}$ | 200 | 200 | 0 |

* Dose corrected for inhomogeneity (see legend for Figure 3*B*).

fabricated from an appropriate metal of optimum thickness and especially designed for clinical use. This development in our laboratory has been adequately described in Part 1 of this report (preceding article).

The final product was a tiny cartridge of gold, 1.6 mm.×10 mm., easily cut from gold tubing of 10 mils wall thickness and a lumen of approximately 1.02 mm. diame-

(*Text continued on page 579*)



treatment to 6,000 r also proved ineffectual. It became imperative to determine with accuracy all additional dosage if we were to utilize safely the cobalt 60 beam and intracavitary radium implants. (*F*) Same patient as in *E*. Microdosimeters were attached to an acrylic mold, which was fabricated to fill the defect in the patient's skull. In a "verification" procedure, employing the cobalt 60 beam, the glass rod recorded a dose which varied by only 4.7 per cent from the intended or phantom value.

C
D

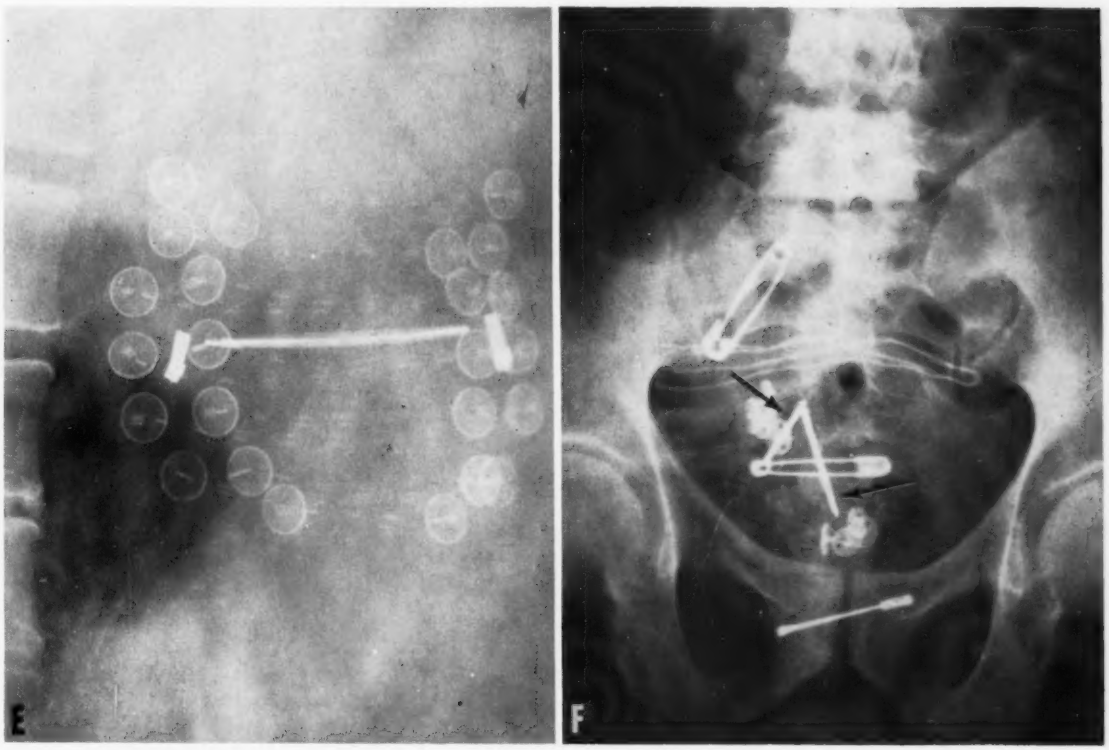


FIG. 2. (*A*) Note this huge recurrent carcinoma in the left neck of a patient recently operated upon for carcinoma of the larynx. The striking variation in the contour of this ulcerating and exophytic tumor made precise dosage calculation difficult. (*B*) Same patient as in *A*. A glass rod in a hollow radium needle has been implanted in the tumor to provide accurate *in vivo* dosage measurement. The measured value proved to be within 5 per cent of the calculated dose, using the cobalt 60 teletherapy beam. (*C*) Note the three microdosimeters in tandem in a No. 8 French polyvinyl feeding catheter, to monitor rotational therapy for esophageal carcinoma. The measured dose in the 1,000 kv. beam was within less than 5 per cent of the phantom value at all three dosimeter levels. (*D*) Pelvic roentgenogram illustrates a unique attempt to measure radium dosage at point B in the left parametrium of a patient receiving treatment for cervical carcinoma (courtesy Dr. Gray Twombly). Note the 4 cm. hollow radium needle (containing glass rods) implanted at point B through the patient's vagina (left lateral fornix). We intended to deliver 1,000 r to this site in each of 2 successive implants. The recorded dose was 990 r while the calculated dose (through analytical geometry) was exactly 960 r. Note another needle in a catheter in the bladder, carrying its dosimeter load. Rectal dosimeters have been similarly employed in our Radiation Clinic. Further, dosage at point A can be easily acquired by means of interstitial rod implant or by a catheter (with rod) in the ureter. (*E*) This roentgenogram shows a two-plane, iridium 192 seed implant (in nylon thread) in a large metastatic carcinoma on the chest wall. Four dosimeters, mounted in individual gold shields, have been placed in tandem, in a plastic tube, through the midplane of the implant. The recorded values varied by only 2.4 per cent from the calculated dose. (*F*) A patient with carcinoma of the bladder at the trigone required a single plane iridium 192 implant for a planned tumor dose of 6,000 r in six days. One hollow radium needle containing a dosimeter was placed directly in the center of the implant and withdrawn on the fourth day as a monitoring maneuver. The dosimeter read 4,200 r, compared with a calculated dose of 4,000 r, a variation of only 5 per cent. This variation can be accounted for by the curvature in the bladder, whereas the dose calculations were based on the Paterson-Parker figures for a flat or planar implant. A second needle with dosimeter is seen at the periphery of the implant.

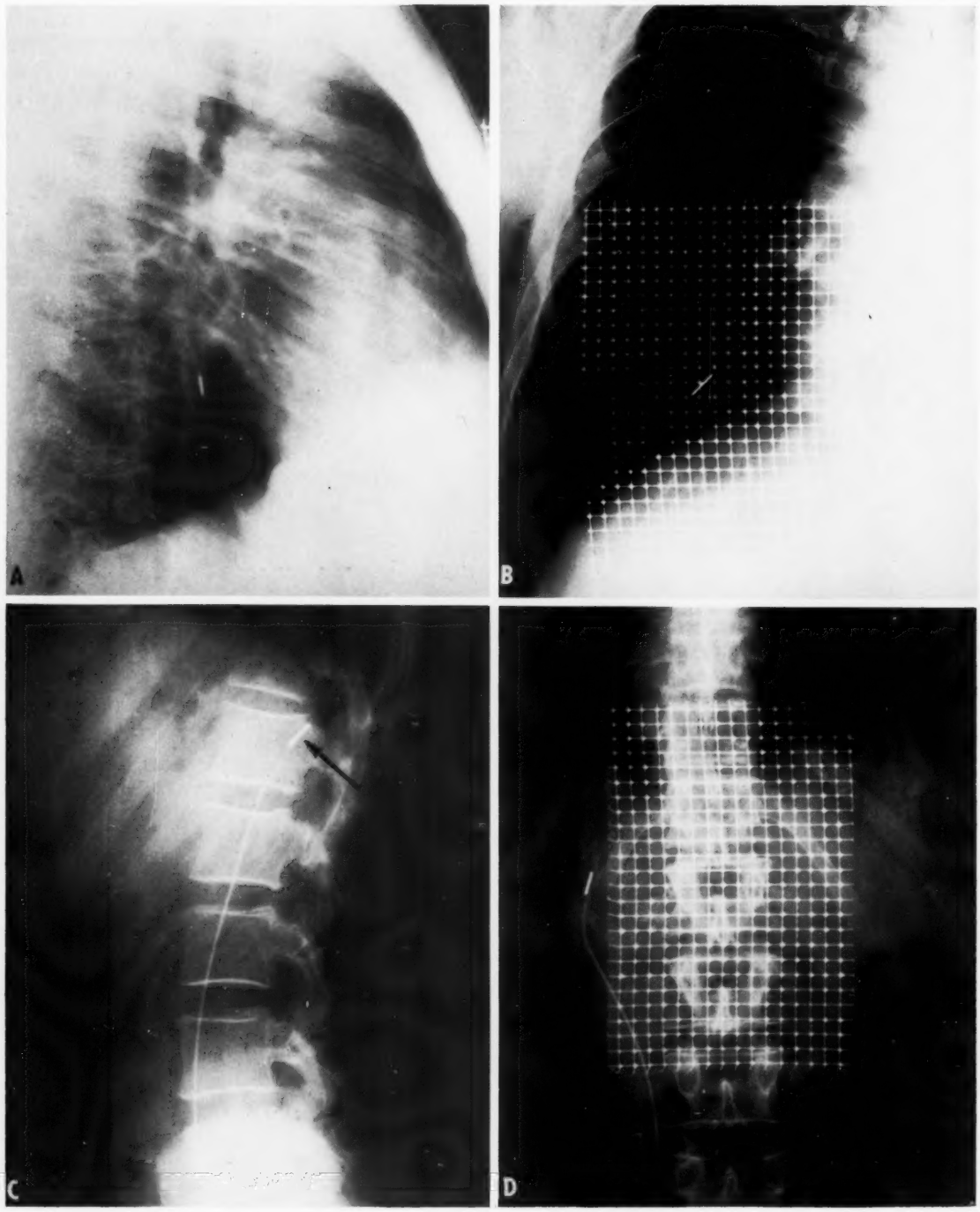



Fig. 3. (*A*) In this lateral chest roentgenogram is shown a gold-shielded dosimeter in a plastic tube, lying within the right lower lobe bronchus of an individual with a normal right lung. With this system, we are studying the inhomogeneity factor, so important in the radiation treatment of intrathoracic neoplasms. (*B*) Same patient as in *A*. The wire grid serves to outline the treatment portal as well as to orient the detector in the beam. A lateral roentgenogram is also made in this manner. The measured dose from the cobalt 60 exposure was 248 r. The corrected calculation was 239 r, a variation of only 3.7 per cent (reference to inhomogeneity correction tables of Jacobson suggested a correction value of 15 per cent[9]). A study of

➟

ter. One end was sealed and the other carried a tiny screw cap. After many trials a system was evolved to permit entry of an optimum level of scattered radiation; four tiny holes, each at 90° from the other, were drilled in the midsection of the shaft. For ready identification, each gold cartridge was engraved in an orderly numbered system.

B. SPECIAL ADVANTAGES

With the gold-shielded glass rod we achieved:

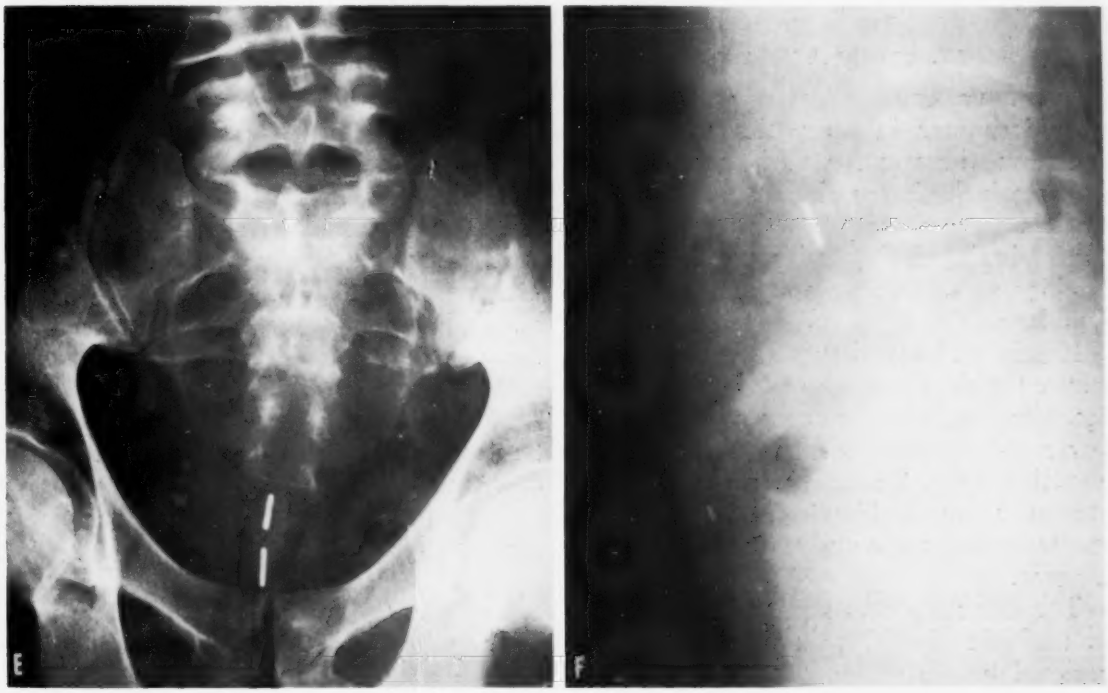
1. Independence of therapeutic energy or modality employed—from 250 kv. to 2,000 kv., including radium, radon, cobalt 60, cesium 137, iridium 192 and other high energy sources. Therapy with different modalities can thus be measured (and added) in the same patient in the same lesion, with confidence in the values. This eliminates the requirement of calibrating a dosimeter against each specific therapy source.

2. Independence of portal size—from the smallest to the largest used in clinical practice, including total body exposure.

3. Independence of depth in tumor or tissue—from the skin to 20 cm.

4. Reduction in probability for contamination and of damage of glass rods.

5. Easy identification by means of roentgenography and by engraved numbers.




the lung inhomogeneity problem has been initiated. (*C*) A dosimeter was successfully placed within this patient's renal pelvis, using a No. 8 French polyvinyl catheter, stiffened with a slender conventional urethral catheter. The urine drained well while radiation therapy was administered. (*D*) The grid wire represents the uppermost portal employed in the postoperative cobalt 60 irradiation of this patient's para-aortic lymph nodes after removal of a testicular seminoma. It is of interest that the dose measured at the renal pelvis was only 15 per cent of the tumor dose in the central axis of the beam. The study of renal dosage is being extended. (*E*) This patient is to receive radiation treatment for cancer of the bladder using the cobalt 60 rotational beam. A pair of dosimeters in their gold capsules has been inserted via urethral catheter for precise recording of the tumor dose. (*F*) In this patient with an advanced carcinoma of the bladder, a microdosimeter has been placed within the abdominal aorta via the femoral artery in an attempt to secure a recording of the dose delivered to the para-aortic lymph nodes.

6. Increased useful range of dosimeter —from 50 r to 20,000 r.

7. Economical use (completely fabricated gold cartridges cost about three dollars each).

8. Nontoxicity in human tissues—even after protracted implantation periods for cumulative dose records.

9. Miniaturization to a point wherein nearly all body spaces and tissues are pregnable to dose recording.

10. Accuracy with variations of only ±5 per cent clinically and ±1–2 per cent experimentally.

### C. DISADVANTAGES

There appeared to be no significant deficiencies of the gold-shielded glass rod system.

## III. CLINICAL TRIALS

We have employed the gold-shielded microdosimeter in 40 patients receiving radiation therapy for various malignant diseases, including carcinoma of the kidney, testicle, larynx, tongue, stomach, antrum, breast, brain, cervix, vagina, esophagus and bladder, soft tissue sarcoma and malignant lymphoma.

Nearly all body tissues and spaces were entered with relative ease for *in vivo* dose recording, including the ureter, renal pelvis, parametrium, mandible, nasopharynx, paranasal sinuses, trachea, bronchus, brain, stomach, bowel, bladder, uterus, heart, mediastinum, aorta and the general vascular tree.

The detectors were stationed singly and in multiples in (a) primary tumors, (b) regional lymph nodes, (c) distant metastases and (d) nearly all normal structures in the path of the therapy beam. In these stations they were employed interstitially, intravascularly, intracavitarily and on the surface, for dose verification and surveillance. After exposure to radiation, the glass rods were removed from their gold shields and placed in the reader.

Conventional and easily available devices were utilized to carry the shielded dosimeters, such as plastic tubing, hollow radium needles, Foley catheters, Friedman-Lewis catheters, Miller-Abbott tubes, cardiac catheters, etc. One of the most generally useful devices was a simple polyvinyl feeding tube, No. 8 French, costing less than fifty cents. With one or more cartridges tucked into its tip, we have been able to enter the ureters, renal pelvis, uterus, bronchial tree, blood vessels and other important structures hitherto inaccessible to a radiation dosimeter.

The treatment modalities used in this study included orthovoltage (260 kv.), supervoltage (1 mv.), cobalt 60 teletherapy, interstitial radium, radon, and iridium 192. In this energy range, complete linearity and energy independence was observed, regardless of portal size and depth in the body up to 20 cm. Portals up to 600 cm.$^2$ were used. Even when several treatment modalities were employed for the same tumor, the dosimeter summated fractionated doses, with variations of less than ±5 per cent from the calculated or phantom value.

Contamination of the glass and damage to its structure are now rarely encountered in our clinic. The bare glass is gently handled with tiny tweezers and placed in the protective gold shield without difficulty. The x-ray technician takes charge of the loading and unloading, and the preparation and sterilization of needles, catheters and other devices. Cold sterilization (using zephiran) is invariably employed because excessive heat will affect the glass.

## IV. WORK IN PROGRESS

The gold-shielded glass microdosimeter is presently being employed in living human subjects for special investigations such as evaluation of: (1) new treatment planning techniques; (2) assessment of methods for precise beam orientation and patient immobilization; (3) inhomogeneity factors in lung and bone at various energy levels; (4) recording tissue dose in critical normal structures in conventional and experimental treatment plans; (5) dose verification procedures in individual patients under

treatment; (6) dependability of the microdosimeter with use of energy levels up to 100 mv. roentgen rays, high energy electron beams, and a broad spectrum of radioactive isotopes; (7) evaluation of techniques for more effective total body irradiation at high dose levels plus marrow transplants, in patients with advanced malignant disease; and (8) efficiency of the glass microdosimeter in a mixed neutron-gamma beam, a problem of major interest for those planning neutron irradiation for tumors of the brain.

## CONCLUSIONS

1. We have developed a practicable and reliable microdosimeter system for accurate *in vivo* human dosimetry in radiation therapy.

2. This system is immediately adaptable to routine clinical use and experimental studies.

3. It has been employed successfully in nearly all body tissues and spaces in cancer patients receiving ionizing radiation.

4. The detectors consist of tiny photoluminescent glass cylinders enclosed in miniature gold cartridges which can be easily and quickly fabricated.

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Bronx 68, New York

For their assistance in this investigation, we wish to thank Drs. Schulman and Attix of the U.S. Naval Research Laboratory, Dr. Max Pleasure, Chief of our Dental Service, and Mr. Louis Maddalone, Mold Technologist in our Radiation Clinic.

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# EDITORIALS

## FORTY-THIRD ANNUAL MEETING OF THE AMERICAN RADIUM SOCIETY

THE American Radium Society was organized forty-five years ago, in June, 1916, during an Annual Meeting of the American Medical Association, by 24 physicians interested in radium therapy, under the leadership of W. H. B. Aikens of Toronto, Canada, acting as temporary president, and R. E. Loucks of Detroit, Michigan, as the temporary secretary. H. K. Pancoast, M.D., was in charge of the dinner and Henry Schmitz, M.D., of Chicago, chairmanned a Committee on Constitution and Bylaws. The name chosen was "The American Radium Society."

The object of the Society was, and still is, "to promote the scientific study of radium and other sources of ionizing radiation in relation to their physical properties and their therapeutic application" and to maintain the high ethical standard among those using these agents for treatment.

The Forty-Third Annual Meeting (during World War II some meetings were omitted) will be held at the Broadmoor Hotel in Colorado Springs, Colorado, on Wednesday through Saturday, 10, 11, 12, and 13 May, 1961.

On Wednesday, 10 May, 1961, the Executive Committee will meet and in the afternoon there will be general registration.

The first Executive Business Session will be held during a breakfast meeting for members of the Society on Thursday morning, 11 May. At 9:00 A.M. the Scientific Program opens with an Address on "The Concept of a Cure" by Dr. Fred C. D. Collier, Professor of Surgical Pathology, University of Alabama Medical School, Birmingham, Alabama. Dr. Collier will be introduced by Dr. Luther W. Brady, Jr., Chief of the Radiotherapy Division of The Hahnemann Medical College and Hospital of Philadelphia. Dr. Collier's Address will set the tone and provide the Keynote of the Meeting.

A critical survey of the current methods of treatment and results obtained in carcinoma of the ovary and brain tumors will highlight the program, and some new aspects of the physics of radiation therapy as well as newer ideas of treatment will be presented.

The Janeway Lecture will be delivered by a prominent Canadian neighbor and member of the Society, Dr. Clifford L. Ash, Director of the Ontario Cancer Institute at Toronto incorporating the Princess Margaret Hospital, and Professor of Radiotherapy at the University of Toronto. Dr. Ash's address, which is most timely, is entitled "Intra-Oral Cancer, a Twenty-five Year Study."

A Social Hour will be held on Thursday evening sponsored by the Radium Chemical Company. On Friday evening, there will be a reception, followed by the Annual Banquet. The past presidents of the American Radium Society will be honored with ceremonies and "high jinks" at a special table during this banquet. The Koshare Indians will give a series of colorful tribal pageants and dances after the banquet.

Three distinguished French colleagues will participate in the program. Professor A. Lacassagne, one of the earliest investigators in the field of radiobiology, will discuss new experimental work on carcinoma of the liver. Dr. A. Ennuyer and Dr. Bernard Pierquin of the Fondation Curie, Paris, France, will deal with topics, the titles of which will be announced in the final program.

Colorado Springs is particularly beautiful in the spring month of May. The charming old Broadmoor Hotel is nestled beside a lake in the foothills of the Rocky Mountains. Pike's Peak, with an altitude of 6,500 feet, is within sight to the north and the Air Force Academy is located in the foothills.

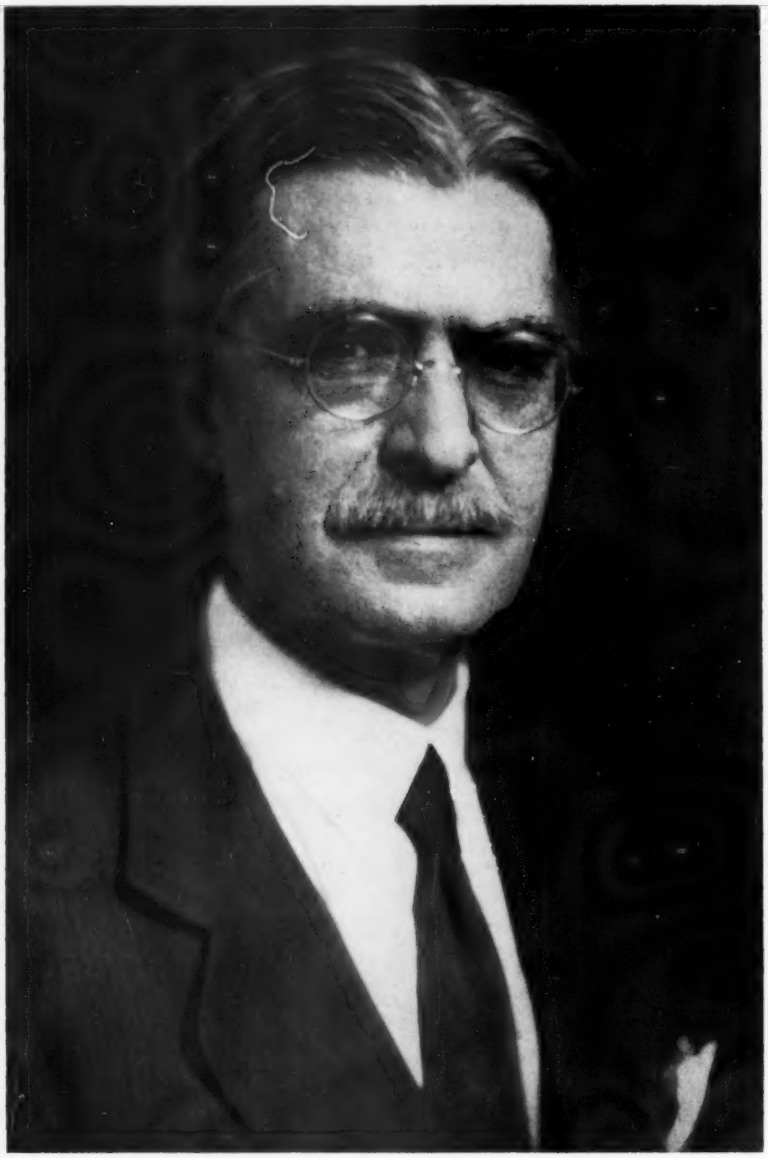
The Broadmoor is modernized in every way. A new auditorium with a parabolic roof meets every requirement for a convention. The charm, services and facilities of the hotel ensure a very pleasant visit. Boating, water skiing, a heated swimming pool and an indoor ice rink give opportunities for varied recreation. On any afternoon an organized scenic tour through the mountains and valleys can be arranged.

Registration will begin on Wednesday, 10 May, from 2:00 P.M. to 5:00 P.M. and will continue throughout the duration of the meeting.

You are urged to make hotel reservations through Dr. Juan A. del Regato early, since the list will be closed 15 April, 1961. Accommodations at motor courts and other hotels may be requested as well.

The officers of the American Radium Society cordially invite you and urge you to attend its Forty-third Annual Meeting in the beautiful surroundings of the Broadmoor Hotel in the foothills of the Rocky Mountains.

Jesshill Love, M.D., *President*
The American Radium Society
Memorial Cancer Foundation
2315 Bath Street
Santa Barbara, California



# WILLIAM STELL NEWCOMET
## 1872–1960

WITH the passing of William Stell Newcomet on September 9, 1960, Radiology lost another distinguished pioneer.

Born in Philadelphia, Pennsylvania, on July 20, 1872, the son of Henry Walborn Newcomet and Elizabeth Kesia Stell, Dr. Newcomet received his primary education in the schools of Philadelphia. He attended Friends' Girard Avenue School and the Lauderbach Academy. At the age of thirteen, following his father's early death, his mother decided to take her three children to Europe. While there, William New-

comet enrolled at the University of Berlin (1888–1889) and remained after his family returned home. His major interest was in chemistry. The instructions that he received in German and in chemistry were to be of great value to him in his medical career. In 1890, he returned to Philadelphia and matriculated at the Medical School of the University of Pennsylvania, from which he received his M.D. degree in 1893. After an internship at St. Agnes Hospital in Philadelphia, he entered general practice and became associated with the St. Agnes Hospital and the Rush Hospital for Consumption. He was also the attending physician to the House of the Good Shepherd.

At the Rush Hospital, in 1898, Dr. Newcomet became interested in the employment of x-rays in the study of the chest, and in 1899, he became the director of the X-Ray Department of the Presbyterian Hospital in Philadelphia, a position he held for approximately fifty years.

In 1904 the Oncologic Hospital of Philadelphia was organized and Dr. Newcomet was placed in charge of the X-Ray Department. Shortly thereafter, in 1907, radium was acquired for the first time in that institution. Dr. Newcomet constructed the radon apparatus in this institution in 1921.

In 1916, Dr. Newcomet joined the Red Cross unit of the Presbyterian Hospital and entered the Army as First Lieutenant on June 15, 1917. From this period until 1919, he served at Camp Greenleaf and Camp Gordon in Georgia, as Acting Adjutant in charge of the X-Ray Department, Instructor in the Rules of the Army Survey and Court Officer. From February, 1919, to April 29, 1919, he was in charge of the X-Ray Department at General Hospital, No. 35, West Baden, Indiana, when he retired as a Major. He was advanced to a Lieutenant Colonel in the Reserve Corps in 1920.

Dr. Newcomet was primarily interested in organized medicine and found time to actively participate in many organizations. His affiliations included: The Philadelphia County Medical Society, Vice President and Member of the Board of Directors for eleven years; Fellow of the College of Physicians of Philadelphia; President, West Branch Philadelphia County Society, 1917; Fourth Vice President, American Roentgen Ray Society, 1909; Secretary of American Radium Society and its President in 1925; Fellow of the College of Radiology; Diplomate of the American Board of Radiology; Member of the Franklin Institute (1944–1960); Member of the American and Philadelphia Mineralogical Societies; and an active and devoted Mason and Past Master in the Stephen Girard Lodge 450, Pennsylvania.

Dr. Newcomet was well known to earlier generations of radiologists. He was a quiet and gentle physician with a good sense of humor and was liked by everyone. His ideals were on a high plane. His knowledge of physics and chemistry provided the background for much of his early work in radium and roentgen therapy. He was well informed on the world's literature and generously contributed to it.

His publications on chest diseases date back to 1899. His contributions on "Treatment of Malignant Disease with X-Rays," in 1903; "Pathological Changes in Tissue under the Influence of the X-Rays" and his book, "Radium and Radiotherapy," published by Lea and Febiger in 1914, have stood the test of time, and many of the observations are in accord with current thinking. Dr. Newcomet's greatest interest probably was in therapy, especially with the use of radium, and he developed a well earned reputation for his work with the care of hemangiomas in children. It should be stated that Dr. Newcomet was one of the very few pioneers who was most cautious and, so far as I know, did not develop any radiation damage changes on his hands, face and/or body.

Dr. Newcomet came from a Pennsylvania-German background. He believed in thrift and in using one's time well. His profession was his chief interest and he rarely took vacations. He had several

hobbies from which he derived great enjoyment. Dr. and Mrs. Newcomet spent many happy hours along the Brandywine, while he sketched that lovely stream. From childhood he was an avid collector of minerals and as he grew older he made trips to many mines and caves to obtain new specimens for his large collection. He was particularly interested in fluorescent minerals and exhibited them under various lights. His hobby of keeping bees on occasion presented problems in his city home when they would swarm and leave for greener pastures.

On April 22, 1897, Dr. Newcomet married Katherine E. Mackeown. His daughter, Mrs. Paul W. Sutro and three grandchildren, survive.

The onset of Dr. Newcomet's terminal illness stemmed from metastatic lesions in the chest secondary to a carcinoma of the colon which had been removed eighteen months before. Death ended the career of a man whose life had been one of achievement and enrichment for himself, his profession and for those who were privileged to know him.

Eugene P. Pendergrass, M.D.

# THE AMERICAN RADIUM SOCIETY

## TENTATIVE PROGRAM

The following is the tentative program arranged by the Program Committee for the Forty-third Annual Meeting of the American Radium Society to be held at the Broadmoor Hotel, Colorado Springs, Colorado, Wednesday through Saturday, 10, 11, 12 and 13 May, 1961.

*Wednesday, 10 May, 1961*

9:00 A.M.–4:00 P.M.
Executive Committee Meeting.

2:00–5:00 P.M.
Registration.

*Thursday, 11 May, 1961*

7:30 A.M.
First Executive breakfast Business Session for members.
Appointment of committees, election of new members.

9:00 A.M. Onward.
Registration

9:00 A.M.
First Scientific Session.
Robert L. Brown, M.D., Chairman.

Opening Ceremonies and Welcome Address. Jesshill Love, M.D., Santa Barbara, California.

Keynote of the Meeting: Concept of a Cure. Fred C. D. Collier, M.D. (by invitation), Birmingham, Alabama.
Introduction of Dr. Collier by Luther W. Brady, Jr., M.D., Philadelphia, Pennsylvania.

Comparative Study of Supervoltage Radiotherapy Techniques in Some Pelvic Malignancies. Jose Noriega, M.D., Mexico City, Mexico.

*Panel Discussion*

A Critical Analysis of Current Therapy of Carcinoma of the Ovary: Natural history of ovarian neoplasms. Is surgery alone adequate? Has postoperative irradiation proven itself? Value of radioisotopes and chemotherapy.
Philip Rubin, M.D., Rochester, N. Y., Moderator.

Panelists: Malcolm B. Dockerty, M.D. (by invitation), Rochester, Minnesota, John G. Masterson, M.D. (by invitation), Brooklyn, New York, Howard B. Latourette, M.D., Iowa City, Iowa, Vera M. Dalley, M.D. (by invitation), London, England, and others.

The Influence of the Time Factor on the Dose Response Curve. Lucille A. DuSault, A.B., Detroit, Michigan.

Observations of Radioresponse of some "Radioresistant" Neoplasms. Franz J. Buschke, M.D., San Francisco, California.

12:15 P.M.
Recess.

12:30 P.M.
Luncheon for members, guests and wives.
*T. Christen, the First Investigator of the HVL.* Speaker, E. Dale Trout, B.S., Sc.D., Milwaukee, Wisconsin.

2:00 P.M.
Victor Marcial, M.D., Chairman.

*Symposium*

Radiosensitivity and Radiocurability Judged by Microscopical Techniques.
Joseph L. Morton, M.D., Moderator.

The Cytologic Prognosis in Cancer of the Cervix. Ruth M. Graham, Sc.D. (by invitation), Buffalo, New York.

Radiosensitivity Testing of Cancer of the Cervix. Saul B. Gusberg, M.D., New York, New York.

Can Radiosensitivity and Histopathology Be Correlated? Arthur T. Hertig, M.D. (by invitation), Boston, Massachusetts.

Incidence and Treatment of Radiation Necrosis of the Intraoral Cavity. William S. MacComb, M.D., Houston, Texas.

(Title to be announced.) Dr. Bernard Pierquin (by invitation), Villejuif (Seine), France.

5:30 P.M.
The Janeway Lecture. Clifford Ash, M.D., Director, Ontario Cancer Institute, Toron-

to; Professor of Radiotheraphy, University of Toronto. Intra-Oral Cancer, a Twenty-five Year Study.

6:30 P.M.
Social Hour.

7:30 P.M.
Dinner *ad libitum*.

*Friday, 12 May, 1961*

7:30 A.M.
Second Executive breakfast Business Session for members.
Committee reports. Old and new business. Introduction of new members. Required attendance of all new members.

9:00 A.M. Onward.
Registration.

9:00 A.M.
Second Scientific Session.
Charles Stetson, M.D., Chairman.

Ten Year Evaluation of the Treatment of Bone Metastasis from Breast and Prostate Carcinoma Using $P^{32}$ and Testosterone. Jack G. S. Maxfield, M.D., and J. R. Maxfield, Jr., M.D., Dallas, Texas.

Complications in the High Dose Total Pelvic Irradiation of Female Pelvic Cancer. Paul M. Chau, M.D. (by invitation), Gilbert H. Fletcher, M.D., and Felix N. Rutledge, M.D. (by invitation), Houston, Texas.

The Intravenous Pyelogram and Carcinoma of the Cervix. Richard W. Stander, M.D. (by invitation), and Robert K. Rhamey, M.D. (by invitation), Indianapolis, Indiana.

Cobalt 60 Tangential Dosimetry. Harold E. Johns, Ph.D., Toronto, Ontario.

(Title to be announced.) Dr. A. Ennuyer (by invitation), Paris, France.

Hemipelvectomy in the Treatment of Advanced Cancer. Theodore R. Miller, M.D., New York, New York.

A Cesium Unit for Head and Neck Therapy. M. Lederman, M.D., London, England.

Clinical and Biological Studies of Actinomycin D and Radiation. Giulio J. D'Angio, M.D. (by invitation), Boston, Massachusetts.

Low-Level X Irradiation and the Very Early Mammalian Embryo. Roberts Rugh, M.D. (by invitation), New York, New York.

Cancer Arising Many Years after Radiation Therapy of Benign Lesions in the Cervical Region. John M. Hanford, M.D. (by invitation), and Edith H. Quimby, Sc.D.

Honored speaker of the Forty-third Annual Meeting of the American Radium Society. Experimental Carcinoma of the Liver. Professor A. Lacassagne, Paris, France.

12:15 P.M.
Recess.

2:00 P.M.
Tour of the United States Air Force Academy.

6:30 P.M.
Reception.

7:30 P.M.
Annual Banquet.
Presentation of the Janeway Medal.
Table honoring the past Presidents of the American Radium Society.
Presentation of Mementos to past Presidents.
Spectacular dance revue by the Koshare Indians.

*Saturday, 13 May, 1961*

9:00 A.M. Onward.
Registration.

9:00 A.M.
Third Scientific Session.
Gilbert H. Fletcher, M.D., Chairman.

Board of Inquiry. A three man board will be picked to review a series of very unusual cases. Arbitrator, Milton Friedman, M.D., New York, New York.

Radiation Therapy of Brain Tumors. Robert J. Bloor, M.D., and Arch W. Templeton, M.D. (by invitation), Rochester, New York.

Localization of Brain Tumors Using $I^{131}$HSA; Problems of Instrumentation and Technique. Edward B. Schlesinger, M.D. (by invitation), Sheila deBoves, M.S. (by invitation), and Juan Taveras, M.D. (by invitation), New York, New York.

Irradiation of Meningioma. Milton Friedman, M.D., New York, New York.

Should We Treat Glioblastoma Multiforme? Juan M. Taveras, M.D. (by invitation), and J. Lawrence Pool, M.D., New York, New York.

A Three Dimensional Radium Reconstruction Device. Jerome M. Vaeth, M.D., San Francisco, California.

A Moving Picture: "Radium Implantation: Operating Room Techniques." Fernando G. Bloedorn, M.D., and Carlo A. Cuccia, M.D., Baltimore, Maryland.

Distant Metastasis from Oral Cancer. Sidney Rubenfeld, M.D., New York, New York.

Why Go to the Moon? Maj. Gen. David Wade, U.S.A., Commanding Vandenberg Air Force Base, will appoint a discussant to outline the necessity for space travel and investigation.

12:30 P.M.

Third Executive Business Session.

Election of officers. Introduction of new officers.

12:45 P.M.

Luncheon *ad libitum*.

Adjournment.

Papers to be read by title:

Post Radiation Treatment of Total Body Lethal Irradiation with Cell Free Spleen Extract (Pending AEC and USN approval). Friedrich P. Ellinger, M.D., Ph.D. (by invitation), Washington, D. C.

A World Survey of Radioisotope Teletherapy Units (900 units in 50 countries) (Pending approval of the IAEA). Kia-Chi Tsien, B.Sc., M.A., Vienna, Austria.

Radiotherapy in the Luis Razetti Institute of Cancer in Caracas. Raul Vera V., M.D., Caracas, Venezuela.

Address all applications for hotel reservations or correspondence relevant to the meeting to:

Juan A. del Regato, M.D., Chairman of Arrangements
Penrose Cancer Hospital
2200 No. Cascade Avenue
Colorado Springs, Colorado

# NEWS ITEMS

## DAVID ANDERSON-BERRY PRIZE (1961)

A David Anderson-Berry Silver-Gilt Medal, together with a sum of money amounting to not less than one hundred pounds sterling (£100/$280.00), will be awarded in 1961 by the Council of the Royal Society of Edinburgh. The Prize will be awarded for recent work on the effects of x-rays and other forms of radiation on living tissues. Published work will be taken into consideration if submitted to the Society with the application.

In addition to direct application for the Prize, proposals may be made on behalf of others.

Applications and proposals must be in the hands of the General Secretary, Royal Society of Edinburgh, 22/24 George Street, Edinburgh 2, Scotland, not later than March 31, 1961.

## COURSE IN RADIOLOGY OF THE CHEST INDIANA UNIVERSITY

The Department of Radiology of Indiana University School of Medicine announces a postgraduate course in Radiology of the Chest to be given April 6, 7, 8, and 9, 1961, at the Medical Center in Indianapolis.

The course is planned primarily for the general radiologist but is open to all physicians having an interest in this field. Presentations will consist of lectures, panel discussions, and film interpretation conferences, correlating the radiologic, pathologic, and physiologic aspects of various chest conditions encountered in clinical practice.

Guest participants include Drs. Robert P. Barden, William R. Eyler, Benjamin Felson, Melvin M. Figley, C. Allen Good, Jr., John F. Holt, Harold G. Jacobson, and Averill A. Liebow of this country, and Doctor George Simon of London, England.

The subjects for discussion have been arranged so that each day is devoted to one or two subdivisions of the field, thus facilitating a more comprehensive evaluation of lesions of similar origin, as well as those producing similar roentgen findings. Further information regarding this course may be obtained by writing the Director of Postgraduate Medical Education, Indiana University School of Medicine, Indianapolis 7, Indiana.

## UNIVERSITY OF WISCONSIN POSTGRADUATE COURSE ON DISEASES OF THE CHEST

The Departments of Radiology and Pathology of the University of Wisconsin Medical School are sponsoring a Postgraduate Course dealing with Diseases of the Chest on May 11–13 inclusive. The course will consist of lectures and panel discussions covering a variety of diseases of the lungs and heart. It will be given by a panel of guest speakers, both pathologists and radiologists, together with members of the University of Wisconsin Medical School Faculty. Guest speakers include Drs. John A. Campbell, Benjamin Castleman, Jesse E. Edwards, C. A. Good, Averill A. Liebow and Eugene Van Epps. For further information write to William D. Stovall, M.D., Coordinator of Postgraduate Medical Education, University of Wisconsin Medical School, Madison 6, Wisconsin.

## THIRD INTERNATIONAL CONVENTION OF X-RAY TECHNICIANS

The Third International Convention of X-Ray Technicians will meet at the Queen Elizabeth Hotel in Montreal, Quebec, Canada, June 24–29, 1961. Mr. Don Atkins, R.T., is the co-chairman of publicity for this convention.

# BOOK REVIEWS

*Books sent for review are acknowledged under: Books Received. This must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interest of our readers as space permits.*

Radio Terapia. By Giulio Tori. Pp. 693, with 351 illustrations. Prof. R. Patron, Bologna, Italy, 1960.

In the preface to this book, Prof. G. Palmieri notes that most radiology residents relegate radiation therapy to a secondary role and prefer to dedicate much more time and effort to diagnostic radiology. For those who take radiotherapy more seriously, there is a need for texts which, without overemphasis on one or the other facet of radiotherapy, encompass the whole with enough detail to give the residents a secure foundation of study which can be expanded in later years.

Dr. Tori, who is in charge of teaching nuclear physics applied to medicine at the University of Bologna, has attempted this task and has succeeded very well. This book is tailor-made for the training of residents and gives them all the essential facts with a clarity of expression and a completeness of presentation seldom found in teaching manuals.

Dr. Tori begins with the fundamental concepts of matter and energy and with the interaction of energy and matter. This is followed by a discussion of measurements of quantity and quality of radiation. The various types of radiation generators and the natural and artificial radioactivity and its measurement are described.

The second section of the book is devoted to radiobiology, and includes the general effects of radiation on cells and, specifically, the effects of radiation on each tissue. The discussion on the direct effect of radiation on the gonads is amplified by a description of genetic effects. The effects of radiation on pathologic tissues are described in detail.

The third section of the book deals with dosimetry as applied to fixed and mobile beams of radiation, with filters and with grids, and it considers the spatial and chronologic distribution of radiation effects, treatment planning, contraindications, association of radiation therapy with surgery, general and local reaction and prognosis in specific cases.

The fourth section deals with the radiation therapy of various disease entities, beginning with cancer of the lip and ending with functional therapy of hypertension, Raynaud's disease and asthma. It gives detailed instruction on how to conduct treatments and it covers the whole field of the application of radiation therapy. This section is generally excellent, but the emphasis placed on radiation therapy of nonmalignant diseases may be considered excessive by some American radiologists.

An appendix deals with protection of personnel and patients from radiations produced by various agents and at various levels of energy.

This is an excellent book, concise and to the point, and is especially adapted for the instruction of residents. Since Dr. Tori speaks English fluently, it is to be hoped that he will translate this book into the English language for the benefit of English and American residents.

Cesare Gianturco, M.D.

Genetics and Cancer; A Collection of Papers Presented at the Thirteenth Annual Symposium on Fundamental Cancer Research, 1959. Edited by the Staff of The University of Texas M. D. Anderson Hospital and Tumor Institute. Cloth. Price, $8.50. Pp. 459, with numerous illustrations. The University of Texas Press, Austin 12, Texas, 1960.

This volume consists of twenty-two articles by eminent scientists from England, France, Sweden and the United States, an introduction by R. Lee Clark, Jr., Director and Surgeon-in-Chief, the University of Texas M. D. Anderson Hospital and Tumor Institute, Houston, Texas, and a summary by Howard B. Andervont, National Cancer Institute, Bethesda, Maryland. Together, they constitute a thorough and authoritative review of the topics considered.

The material is divided into six sections. The first, *Genetic Theory of Cancer Etiology*, includes three papers on plasmagenes, somatic mutations and lysogens. Six papers are devoted to the next subject, *Fundamental Aspects of Genetics in Carcinogenesis*, and five to the section on *Gene Interaction in Neoplastic Growth*. The

Bertner Foundation Lecture was part of this symposium and is entitled, "The Role of Virus and Host in Determining the Host Reaction to the Fibroma-Myxoma Virus Complex." Three papers deal with the *Genetic Basis of Cell Resistance*, and the four papers on *Heredity and Human Cancer* point out the progress and methods of study in human genetics, and the genetic consideration in human cancer.

It should be added that this volume brings together many concepts on the all important question of genetics and cancer. Conversely, because of the ever increasing fundamental knowledge in this field, many modifications and changes in these concepts may be anticipated in the near future.

Johanna Blumel, Ph.D.

Radiologische Exploration des Bronchus. By Dr. S. Di Rienzo, Professor für Radiologie an den Universitätskliniken Cordoba; and Dr. H. H. Weber, Facharzt für Radiologie, Bern. Cloth. Price, $12.85. Pp. 281, with 268 illustrations. Georg Thieme Verlag, Herdweg 63, Stuttgart, Germany, 1960. In the U.S.A. and Canada, Intercontinental Medical Book Corporation, New York 16, N. Y.

The construction of the walls of the bronchi and bronchioles makes it possible for them to have physiologic motion and thus to dilate and to constrict. The embryology, histology, and anatomy of the bronchial system are described briefly. There are good illustrations of the bronchopulmonary segments.

Dr. Di Rienzo is well known for his technique in bronchography using serial roentgenography under fluoroscopic control. He aims to get the early, intermediate, and late phases of filling of the bronchi in each case. He claims that "alveolar" filling is possible only with the use of low viscosity contrast material. The significance of respiration and coughing regarding the size of the bronchial lumen and visualization of pathologic processes is very well demonstrated.

The value of bronchography in cases of congenital anomalies of the bronchi, asthma and emphysema and, of course, in bronchiectasis is discussed *in extenso*. In asthma there are, among other findings, a narrowing of all the bronchi of the second, third, and fourth order, a slow progression of the contrast material, considerable stasis in the small bronchi, and failure of filling of the acini. The appearance of the bronchial tree in Echinococcus of the lung is discussed in great detail with numerous beautiful illustrations of some of the authors' cases.

Bronchography is especially valuable in the early diagnosis of bronchogenic carcinoma in that it enables one to study the physiologic and pathologic dynamics of the normal and abnormal bronchi. The exact location and number of lung abscesses can be discovered with bronchographic study; similarly, with empyema. This method of study is also valuable in observing the postoperative bronchial stump.

Samuel Richman, M.D.

Medical X-Ray Technique; Principles and Applications. By G. J. van der Plaats, Chief Radiologist of the X-Ray Department at St. Annadal Hospital, Maastricht, and former Professor of Radiology in the University of Groningen. Cloth. Price, $10.00. Pp. 480, with 213 illustrations. The Macmillan Company, 50 Fifth Avenue, New York 11, N. Y., 1959.

This work gives a thorough, at times quite technical, description of the operation and construction of most roentgen-ray equipment and accessories in use today. It is written for the technician and provides him with a broad, detailed understanding of these tools. The author presupposes a knowledge of basic physical concepts, but he includes a chapter on radiation physics which is quite comprehensive. Throughout the book, the tone is scientific and it stresses the physical foundation of this medical field, since the author's concern here is not with teaching the standard roentgenographic techniques and positions.

The book is recommended to those technicians who desire a more detailed knowledge of the equipment they use daily in diagnosis and therapy. Radiologists may want to add this volume to their libraries for the same reason.

David Morse, Jr., M.D.

Pneumostratigrafia Cerebrale Normale. By M. Lenzi, G. C. Canossi, and G. Bassani. Price, L. 3,000. Pp. 92, with 57 illustrations. Minerva Medica, Società Tipografica Editrice, Bologna, Italy, 1959.

For several years, Professor Lenzi and his coworkers have applied laminagraphy to differentiate the superimposed and confusing shadows usually seen at encephalography.

This work is essentially an atlas in which normal laminagrams made at encephalographic

examination, taken serially at various levels, are shown and interpreted by schematic drawings with labelled structures. This approach is very satisfactory. The legends are printed both in Italian and in English, making this book useful for readers of the English language.

The atlas proper is preceded by a short text explaining the principles involved and the techniques employed. In this text the authors describe their method of fractionated gas filling and the special laminagraphic apparatus which they have developed for this type of work.

C. Gianturco, M.D.

Röntgenanatomie. By Prof. Dr. med. D. Nagy, Vorstand des Institutes für chirurgische Anatomie und experimentelle Chirurgie der medizinischen Universität, Budapest. Cloth. Pp. 509, with 545 illustrations. Akadémiai Kiadó, Budapest, 1959.

This book on roentgen anatomy exemplifies the attention to detail and thoroughness of coverage usually given to a subject by most Continental writers. The author illustrates each anatomic region by means of photographs to show the positions utilized for each examination. Photographs and drawings depict the relationships between surface landmarks and underlying structures. Anatomic dissections in clear detail further aid in revealing structural relationships.

The book is profusely illustrated with negative image roentgenograms which are more familiar to us than the positive image reproductions often found in foreign texts. They are of the highest quality throughout the book.

Of particular value is the chapter dealing with the anatomy of the pulmonary segments, bronchi and vessels; it is well illustrated with bronchograms and laminagrams. Photographs of the dried skull in various projections supplemented by roentgenograms of these specimens and the living subject are effectively used in another outstanding chapter.

This book is an excellent German text on the subject of roentgen anatomy and an especially fine example of quality in the reproduction of medical material.

David Morse, Jr., M.D.

## BOOKS RECEIVED

Strahlenschutz in Klinik und Ärztlicher Praxis. By Prof. Dr. med. Werner Lorenz, Oberarzt am Röntgen- und Strahleninstitut der Johannes Gutenberg, Universität Mainz. Cloth. Price, $15.70. Pp. 259, with 62 illustrations. Georg Thieme Verlag, Herdweg 63, Stuttgart, Germany, 1961. In the U.S.A. and Canada, Intercontinental Medical Book Corporation, New York 16, N. Y.

Technik der Röntgendiagnostik. By Priv.-Doz. Dr. Hanno Poppe, Leiter des Röntgeninstituts der Chirurg. Univ.-Klinik Göttingen, Oberarzt der Klinik; Ilse Lohstöter, 1. Med.-techn. Assistentin des Röntgeninstituts der Chirurg. Univ.-Klinik Göttingen; and Dr. Ph. Lauwers, Direktor der Abt. für Röntgen und wissenschaftliche Anwendungen Gevaert Photo-Producten N. V. Mortsel (Antwerpen), Belgium. Cloth. Price, $20.95. Pp. 683, with 328 illustrations. Georg Thieme Verlag, Herdweg 63, Stuttgart, Germany, 1961. In the U.S.A. and Canada, Intercontinental Medical Book Corporation, New York 16, N. Y.

Annual Review of Nuclear Science. Volume 10. Edited by Emilio Segrè, University of California; Gerhart Friedlander, Brookhaven National Laboratory; and Walter E. Meyerhof, Stanford University. Cloth. Price, $7.00. Pp. 617. Annual Reviews, Inc., 231 Grant Ave., Palo Alto, Calif., 1960.

The Year Book of Radiology (1960–1961 Year Book Series). Edited by John Floyd Holt, M.D., Professor, Department of Radiology, University of Michigan; Walter M. Whitehouse, M.D., Associate Professor, Department of Radiology, University of Michigan; Harold W. Jacox, M.D., Professor of Radiology, College of Physicians and Surgeons, Columbia University; Chief, Radiation Therapy Division, Radiologic Service, Presbyterian Hospital, New York City; and Morton M. Kligerman, M.D., Professor of Radiology and Chairman of the Department of Radiology, Yale University School of Medicine, Director of Radiology, Grace-New Haven Community Hospital. Cloth. Price, $11.00. Pp. 441, with 305 illustrations. Year Book Publishers, Inc., 200 E. Illinois St., Chicago, Ill., 1960.

Congenital Malformations of the Heart; Volume I: General Considerations. Second edition. By Helen B. Taussig, M.D., Professor of Pediatrics, Johns Hopkins University School of Medicine; Physician-in-Charge, Cardiac Clinic, Harriet Lane Home, Johns Hopkins Hospital. Cloth. Price, $4.75. Pp. 204, with numerous illustrations. Published for The Commonwealth Fund by Harvard University Press, Cambridge 38, Mass., 1960.

Comparative Anatomy, Pathology and Roentgenology of the Breast. By Helen Ingleby, M.D., M.R.C.P., Late Professor of Pathology, Woman's Medical College of Pennsylvania; Research Pathologist on Diseases of the Breast, Albert Einstein Medical Center, Philadelphia, Pennsylvania; and Jacob Gershon-Cohen, M.D., D.Sc. (Med.), Department of Radiology, Albert Einstein Medical Center; Assistant Professor of

Radiology, Graduate School of Medicine, University of Pennsylvania. Cloth. Pp. 472 with 201 illustrations. University of Pennsylvania Press, 3436 Walnut St., Philadelphia 4, Pa., 1960.

La Lumière Bleue; Luminescence par effet de sillage dans les milieux transparents soumis aux radiations de haute énergie. By Lucien Mallet. Paper. Pp. 150, with 53 illustrations. J.-B. Ballière & Fils, Editeurs, 19, Rue Hautefeuille, Paris 6e, France, 1960.

Abridged Scientific Publications from the Kodak Research Laboratories. Volume XXXIV. Paper. Pp. 253. Eastman Kodak Company, Rochester, N. Y., 1960.

Transcript of the Workshop on Bone Densitometry; held at the Stone House, National Institutes of Health, Bethesda, Maryland, December 4, 5, 1959. Paper. Pp. 240. Fels Research Institute for the Study of Human Development, Yellow Springs, Ohio, 1960.

The Scandinavian Journal of Clinical & Laboratory Investigation; Volume 11—Supplementum 44; Cardiopulmonary Hemodynamics in Chronic Lung Disease with Special Reference to Pulmonary Tuberculosis. By Carsten Müller. Paper. Pp. 369. Ejnar Munksgaard, 6 Nörregade, Copenhagen K, Denmark, 1959.

The Scandinavian Journal of Clinical & Laboratory Investigation; Volume 12—Supplementum 45; Influence of Anions and Cations with a Long Hydrocarbon Chain on the Thrombin-Fibrinogen Reaction. By Kristoffer Korsan-Bengtsen. Paper. Pp. 86. Ejnar Munksgaard, 6 Nörregade, Copenhagen K, Denmark, 1960.

The Scandinavian Journal of Clinical & Laboratory Investigation; Volume 12—Supplementum 46; Haemophilia; A Study of Its Laboratory, Clinical, Genetic and Social Aspects Based on Known Haemophiliacs in Finland. By Eero Ikkala. Paper. Pp. 144. Ejnar Munksgaard, 6 Nörregade, Copenhagen K, Denmark, 1960.

The Scandinavian Journal of Clinical & Laboratory Investigation; Volume 12—Supplementum 47; Studies on Urinary Excretion of δ-Aminolaevulic Acid and Other Haem Precursors in Lead Workers and Lead-Intoxicated Rabbits. By Birgitta Haeger-Aronsen. Paper. Pp. 128. Ejnar Munksgaard, 6 Nörregade, Copenhagen K, Denmark, 1960.

The Scandinavian Journal of Clinical & Laboratory Investigation; Volume 12—Supplementum 48; Methodische und Klinische Untersuchungen über die Ausscheidung der 3-Methoxy-4-Hydroxymandelsäure im Urin. By Wilfried von Studnitz. Paper. Pp. 73. Ejnar Munksgaard, 6 Nörregade, Copenhagen K, Denmark, 1960.

The Scandinavian Journal of Clinical & Laboratory Investigation; Volume 12—Supplementum 49; The Direct Diazo Reaction of Bile Pigments in Serum; Experimental and Clinical Studies. By Bertil Nosslin. Paper. Pp. 176. Ejnar Munksgaard, 6 Nörregade, Copenhagen K, Denmark, 1960.

# SOCIETY PROCEEDINGS

## MEETINGS OF RADIOLOGICAL SOCIETIES*

### United States of America

**American Roentgen Ray Society**
*Secretary*, Dr. C. Allen Good, Mayo Clinic, Rochester, Minn. Annual meeting: Deauville Hotel, Miami Beach, Fla., Sept. 26–29, 1961.

**American Radium Society**
*Secretary*, Dr. Charles G. Stetson, 350 Engle Street, Englewood, N. J. Annual meeting: Broadmoor Hotel, Colorado Springs, Colo., May 10–14, 1961.

**Radiological Society of North America**
*Secretary*, Maurice Doyle Frazer, 1037 Stuart Bldg., Lincoln, Neb.
*Treasurer*, Dwight Vincent Needham, 713 E. Genessee St., Syracuse, N. Y. Annual Meeting: Palmer House, Chicago, Ill., Nov. 26–Dec. 1, 1961.

**American College of Radiology**
*Executive Director*, William C. Stronach, 20 N. Wacker Drive, Chicago 6, Illinois. Annual meeting to be announced.

**Section on Radiology, American Medical Association**
*Secretary*, Dr. Clyde A. Stevenson, Sacred Heart Hospital, West 101 Eighth Ave., Spokane 4, Wash. Annual meeting: New York City, June 26–30, 1961.

**American Board of Radiology**
*Secretary*, Dr. H. Dabney Kerr. Correspondence should be directed to Kahler Hotel Building. Rochester, Minn. The Spring 1961 examination will be held at the Denver Hilton Hotel, Denver, Colorado, June 19–22, inclusive; the deadline for filing applications was January 1, 1961. There will be no Special Examination in Nuclear Medicine. The Fall 1961 examination will be held at the Shoreham Hotel, Washington, D. C., December 4–7, inclusive; the deadline for filing applications is July 1, 1961. A Special Examination in Nuclear Medicine will be offered if there are sufficient applications.

**Tenth International Congress of Radiology**
*Secretary-General*, Dr. Carleton B. Peirce, Royal Victoria Hospital, Montreal 2, Quebec, Canada. Meets in Montreal, Aug. 26–Sept. 1, 1962.

**Seventh Inter-American Congress of Radiology**
*Counselor for the United States*, Dr. J. A. del Regato, Penrose Cancer Hospital, 2200 North Cascade Avenue, Colorado Springs, Colorado. The meeting will be held in São Paulo, Brazil, September 3–10, 1961.
*Secretary-General*, Dr. Walter Bomfim-Pontes, Rua Cesario Motta, No. 112, São Paulo.

**Alabama Radiological Society**
*Secretary*, Dr. J. A. Meadows, Jr., Medical Arts Bldg., Birmingham 5, Ala. Meets time and place Alabama State Medical Association.

**American Nuclear Society**
*Executive-Secretary*, Octave J. Du Temple, 86 E. Randolph St., Chicago, Ill.

**Arizona Radiological Society**
*Secretary*, Dr. Don E. Matthieson, 926 East McDowell Rd., Phoenix, Ariz. Two regular meetings a year. Annual meeting at time and place of State Medical Association and interim meeting six months later.

**Arkansas Radiological Society**
*Secretary*, Dr. J. B. Scruggs, Arkansas Baptist Hospital, Little Rock, Ark. Meets every three months and also at time and place of State Medical Association.

**Association of University Radiologists**
*Secretary*, Dr. Melvin M. Figley, Department of Radiology, University of Washington, Seattle 5, Wash. Annual meeting to be announced.

**Atlanta Radiological Society**
*Secretary*, Dr. Wilson T. Edenfield, 35 Linden Ave., N.E., Atlanta 8, Ga. Meets monthly, except during three summer months, on second Friday evening.

**Blockly Radiological Society**
*Secretary*, Dr. Samuel Finkelman, 101 S. Twentieth St. Philadelphia, Pa.

**Brooklyn Radiological Society**
*Secretary*, Dr. Joseph Arcomano, 168 Clinton St., Brooklyn 1, N. Y. Meets first Thursday of each month October through May.

**Buffalo Radiological Society**
*Secretary*, Dr. Kenneth H. Seagrave, 537 Delaware Ave., Buffalo 2, N. Y. Meets second Monday evening each month, October to May inclusive.

**Central New York Radiological Society**
*Secretary*, Dr. Joseph A. Head, 150 Marshall St., Syracuse, N. Y. Meets first Monday each month October through May.

**Central Ohio Radiological Society**
*Secretary*, Dr. Robert L. Freidman, Grant Hospital, Columbus, Ohio. Meets at 6:30 P.M. on second Thursday of October, November, January, March and May at Fort Hayes Hotel, Columbus, Ohio.

**Central Society of Nuclear Medicine**
*Secretary*, Dr. Robert S. Landauer, Radiation Center Building, 1903 West Harrison St., Chicago 12, Ill.

**Chicago Roentgen Society**
*Secretary*, Dr. William F. Hutson, 5145 N. California Ave., Chicago, Ill. Meets second Thursday of each month, October to April except December at the Sheraton Hotel at 8:00 P.M.

**Cleveland Radiological Society**
*Secretary*, Dr. Norman E. Berman, 14404 S. Park Blvd., Shaker Hgts. 20, Ohio. Meetings at 7:00 P.M. on fourth Monday of each month from October to April at Tudor Arms Hotel.

**Colorado Radiological Society**
*Secretary*, Dr. Bertram L. Pear, 3705 East Colfax Ave., Denver 6, Colo. Meets third Friday of each month at Denver Athletic Club from September through May.

**Connecticut Valley Radiologic Society**
*Secretary*, Dr. James L. Krieger, 85 Jefferson St., Hartford, Conn. Meets first Friday in February and April.

**Dallas-Fort Worth Radiological Society**
*Secretary*, Dr. F. J. Bonte, 5201 Harry Hines Blvd., Dallas 35, Texas. Meets monthly, third Monday, at Greater Fort Worth International Airport at 6:30 P.M.

**Detroit Roentgen Ray and Radium Society**
*Secretary*, Dr. Kenneth L. Krabbenhoft, Harper Hospital, Detroit 1, Mich. Meets monthly first Thursday, October through May, at David Whitney House, 1010 Antietam, at 6:30 P.M.

**East Bay Roentgen Society**
*Secretary*, Dr. Dan Tucker, 434 30th St., Oakland 9, Calif. Meets first Thursday each month at Peralta Hospital, Oakland.

**East Tennessee Radiological Society**
*Secretary*, Dr. J. Marsh Frere, Jr., 205 Medica Arts Building, Knoxville, Tenn. Meets in January and September.

**Eastern Conference of Radiology**
*Secretary*, Arrangements Committee, Dr. Philip Myers, Baltimore City Hospital, Baltimore 24, Md. Annual meeting: Lord Baltimore Hotel, Baltimore, Md., March 9–11, 1961.

*** Secretaries of societies are requested to send timely information promptly to the Editor.**

Eastern Radiological Society
*Secretary*, Dr. John D. Osmond, Jr., Euclid-Glenville Hospital, Cleveland 19, Ohio. Meets at Mid Pines Club Southern Pines, N. C., April 16–19, 1961.

Florida Radiological Society
*Secretary*, Dr. Alfred G. Levin, 837 DuPont Bldg., Miami, Fla. Meets twice annually, in the spring with the annual State Society Meeting, and in the fall.

Florida West Coast Radiological Society
*Secretary-Treasurer*, Dr. Joseph C. Rush, 1800 Druid Rd., Clearwater, Fla.

Georgia Radiological Society
*Secretary*, Dr. George W. Brown, Griffin, Ga. Meets in spring and fall with Annual State Society Meeting.

Greater Miami Radiological Society
*Secretary*, Dr. Donald H. Altman, 2751 Coral Way, Miami, Fla. Meets monthly third Wednesday at 8 P.M. at Jackson Memorial Hospital, Miami, Fla.

Greater St. Louis Radiological Society
*Secretary*, Dr. Harvey A. Humphrey, 462 N. Taylor, St. Louis 8, Mo.

Houston Radiological Society
*Secretary*, Dr. John Douglas Reeve, Texas Medical Center Library, Jesse H. Jones Library Bldg., Houston 25, Texas. Meets last Monday each month, Seminar Room, Doctors' Club of Houston.

Idaho State Radiological Society
*Secretary*, Dr. Claude W. Barrick, St. Alphonsus Hospital, Boise, Idaho. Meets in the Spring and Fall.

Illinois Radiological Society
*Secretary*, Dr. George A. Miller, Carle Hospital Clinic, Urbana, Ill. Meets in spring and fall.

Indiana Roentgen Society, Inc.
*Secretary*, Dr. David E. Wheeler, 1500 North Ritter, Indianapolis, Ind. Meets first Sunday in May and during fall meeting of Indiana State Medical Association.

Iowa Radiological Society
*Secretary*, Dr. L. L. Maher, 1419 Woodland Ave., Des Moines, Iowa. Luncheon and business meeting during annual session of Iowa State Medical Society. The scientific section is held in the autumn.

Kansas Radiological Society
*Secretary*, Dr. Lewis G. Allen, 807 Huron Bldg., Kansas City, Kansas. Meets in spring with State Medical Society, and in winter on call.

Kentucky Radiological Society
*Secretary*, Dr. Robert H. Akers, V. A. Hospital, Louisville 2, Ky. Meets monthly on second Friday at Seelbach Hotel, Louisville.

Kings County Radiological Society
*Secretary*, Dr. Abraham Berens, 1917 Bedford Ave., Brooklyn 25, N. Y. Meets Kings County Med. Soc. Bldg. monthly on fourth Thursday, October to May, 8:45 P.M.

Los Angeles Radiological Society
*Secretary*, Dr. Walter Stilson, 1720 Brooklyn Ave., Los Angeles, Calif. Meets second Wednesday of month in September, November, January, April and June at Los Angeles County Medical Association Building, Los Angeles.

Maine Radiological Society
*Secretary*, Dr. Albert A. Poulin, Thayer Hospital, Waterville, Maine. Meets in June, September, December and April.

Maryland Radiological Society
*Secretary*, Dr. Nathan B. Hyman, 1805 Eutaw Place, Baltimore 17, Md.

Memphis Roentgen Society
*Secretary*, Dr. Hollis H. Halford, Kennedy V.A. Hospital, Department of Radiology, Memphis 15, Tenn. Meets first Monday of each month at John Gaston Hospital.

Miami Valley Radiological Society
*Secretary*, Dr. S. F. Johnson, 2197 Los Arrow Dr., Dayton 9, Ohio. Meets second Friday of fall and winter months.

Mid-Hudson Radiological Society
*Secretary*, Dr. Joseph Sorrentino, St. Francis Hospital, Poughkeepsie, N. Y. Meets 8:30 P.M., fourth Wednesday each month, September to May.

Milwaukee Roentgen Ray Society
*Secretary*, Dr. Joseph F. Wepfer, 5000 W. Chambers St., Milwaukee 10, Wis. Meets monthly on fourth Monday, October through May, at University Club.

Minnesota Radiological Society
*Secretary*, Dr. Donald H. Peterson, 853 Medical Arts Bldg., Minneapolis 2, Minn. Meets three times annually, in fall, winter and spring.

Mississippi Radiological Society
*Secretary*, Dr. Jack K. Goodrich, University Medical Center, Jackson, Miss. Meets third Thursday of each month at Hotel Edwards, Jackson, at 6:00 P.M.

Montana Radiological Society
*Secretary*, Dr. J. K. Boughn, 35 11th Ave., Helena, Montana. Meets at least once a year.

Nassau Radiological Society
*Secretary*, Dr. Alan E. Baum, 100 Nowbridge Rd., Hicksville, N. Y. Meets second Tuesday of the month in February, April, June, October and December.

Nebraska Radiological Society
*Secretary*, Dr. Ronald E. Waggener, The Radiologic Center, Nebraska Methodist Hospital, Omaha 31, Nebraska. Meets third Wednesday of each month at 6 P.M. in Omaha or Lincoln.

New England Roentgen Ray Society
*Secretary*, Dr. Robert E. Wise, 605 Commonwealth Ave., Boston 15, Mass. Meets third Friday of each month, October through May at The Longwood Towers, Brookline, Mass.

New Hampshire Roentgen Ray Society
*Secretary*, Dr. Paul Y. Hasserjian, 1470 Elm St., Manchester, N. H. Meets four to six times yearly.

New York Roentgen Society
*Secretary*, Dr. Albert A. Dunn, 622 W. 168th St., New York, N. Y. Meets monthly on third Monday, New York Academy of Medicine at 4:30 P.M.

North Carolina Radiological Society
*Secretary*, Dr. A. B. Croom, 624 Quaker Lane, High Point, N. C. Meets in the spring and fall each year.

North Dakota Radiological Society
*Secretary*, Dr. R. F. Raasch, Post Office Box 990, Dickinson, North Dakota. Meets at time of State Medical Association meeting. Other meetings arranged on call of the President.

North Florida Radiological Society
*Secretary*, Dr. Charles H. Newell, 800 Miami Road, Jacksonville 7, Fla. Meets quarterly in March, June, September and December.

Northeastern New York Radiological Society
*Secretary*, Dr. Lester I. Citrin, St. Mary's Hospital, Troy, N. Y. Meets in Albany area on second Wednesday of October, November, March and April.

Northern California Radiological Society
*Secretary*, Dr. Rob H. Kirkpatrick, 1219 28th St., Sacramento, Calif. Meets at dinner last Monday of each month, September to June.

Ohio State Radiological Society
*Secretary*, Dr. Paul D. Meyer, 125 S. Grant Ave., Columbus, Ohio. Annual meeting third week end in May, 1961 at Columbus, Ohio.

Oklahoma State Radiological Society
*Secretary*, Dr. E. D Greenberger, Medical Arts Bldg., McAlester, Okla. Meets in January, May and October.

Oregon Radiological Society
*Secretary*, Dr. George R. Satterwhite, 1123 S.W. Yamhill, Portland, Ore. Meets monthly from October to June on the second Wednesday of each month at 8:00 P.M. at the University Club.

Orleans Parish Radiological Society
*Secretary*, Dr. Joseph V. Schlosser, Charity Hospital, New Orleans 13, La. Meets second Tuesday of each month.

Pacific Northwest Radiological Society
*Secretary*, Dr. John N. Burkey, 555 Dental Bldg., Seattle, Wash. Annual meeting: Portland, Oregon, May, 1961.

Pacific Roentgen Society
*Secretary*, Dr. L. H. Garland, 450 Sutter St., San Francisco 8, Calif. Meets annually during meeting of California Medical Association.

Pennsylvania Radiological Society
*Secretary*, Dr. Frederick R. Gilmore, 234 State St., Harrisburg, Pa. Annual meeting: Bedford Springs Hotel, May 26–27, 1961.

Philadelphia Roentgen Ray Society
*Secretary*, Dr. Robert B. Funch, Department of Radiology, Germantown Hospital, Philadelphia 44, Pa. Meets first Thursday of each month, at 5 P.M., from October to May in Thompson Hall, College of Physicians.

Pittsburgh Roentgen Society
*Secretary*, Dr. Ross H. Smith, St. Margaret Memorial Hospital, Forty-Sixth St., Pittsburgh 1, Pa. Meets second Wednesday of month, October through June at Park Schenely Restaurant.

Radiological Section, Baltimore Medical Society
*Secretary*, Dr. James K. V. Willson, 1100 N. Charles St., Baltimore 1, Md. Meets third Tuesday each month, September to May, inclusive.

Radiological Society of Greater Cincinnati
*Secretary*, Dr. Donald Janny, Cincinnati, Ohio. Meets monthly from September to May on first Monday of each month at 7:30 P.M. at the Cincinnati General Hospital.

Radiological Society of Hawaii
*Secretary*, Dr. Philip S. Arthur, 274 Young Hotel Bldg., Honolulu, Hawaii. Meets third Monday of each month at 7:30 P.M.

Radiological Society of Greater Kansas City
*Secretary*, Dr. J. Stewart Whitmore, 1010 Rialto Bldg., Kansas City, Mo. Meets last Friday of each month.

Radiological Society of Kansas City
*Secretary*, Dr. Arthur B. Smith, 800 Argyle Bldg., Kansas City, Mo. Meets third Thursday of each month.

Radiological Society of Louisiana
*Secretary*, Dr. Robyn Hardy, 4324 Magnolia St., New Orleans 15, La. Meets annually during Louisiana State Medical Society meeting.

Radiological Society of New Jersey
*Secretary*, Dr. Austin J. Tidaback, 912 Prospect Ave., Plainfield, N. J. Meets at Atlantic City at time of State Medical Society meeting and in November in Newark, N. J.

Radiological Society of New York State
*Secretary-Treasurer*, Dr Mario C. Gian, 610 Niagara St., Buffalo 1, N. Y. Annual meeting to be announced.

Radiological Society of South Dakota
*Secretary-Treasurer*, Dr. Donald J. Peik, 303 S. Minnesota Ave., Sioux Falls, S. D.

Radiological Society of Southern California
*Secretary*, Dr. Joseph F. Linsman, 436 N. Roxbury Dr., Beverly Hills, Calif.

Redwood Empire Radiological Society
*Secretary*, Dr. Lee E. Titus, 164 W. Napa St., Sonoma, Calif. Meets second Monday every other month.

Richmond County Radiological Society
*Secretary*, Dr. W. F. Hamilton, Jr., University Hospital, Augusta, Ga. Meets first Thursday of each month at various hospitals.

Rochester Roentgen Ray Society, Rochester, N. Y.
*Secretary*, Dr. Robert H Greenlaw, 188 Irvington Rd., Rochester 20, N. Y. Meets at 8:15 P.M. on the last Monday of each month, September through May, at Strong Memorial Hospital.

Rocky Mountain Radiological Society
*Secretary*, Dr. John H. Freed, 4200 East Ninth Ave., Denver 20, Colo. Annual meeting: Denver Hilton Hotel, Denver, Colo., Aug. 10–12, 1961.

San Antonio-Military Radiological Society
*Secretary*, Dr. Hugo F. Elmendorf, Jr., 730 Medical Arts Bldg., San Antonio 5, Texas. Meets third Wednesday each month in Fort Sam Houston Officer's Club at 6:30 P.M.

San Diego Radiological Society
*Secretary*, Dr. Stanley A. Moore, 2466 First Ave., San Diego 1, Calif. Meets first Wednesday of each month at the University Club.

San Francisco Radiological Society
*Secretary*, Dr. M. A. Sisson, 450 Sutter St., San Francisco 8, Calif. Meets quarterly at the San Francisco Medical Society, 250 Masonic Ave., San Francisco 18, Calif.

Section on Radiology, California Medical Association
*Secretary*, Dr. William H. Graham, 630 East Santa Clara St., San Jose, Calif.

Section on Radiology, Connecticut State Medical Society
*Secretary*, Dr. Wayne P. Whitcomb, Hospital of St. Raphael, New Haven, Conn. Meetings are held bimonthly.

Section on Radiology, Medical Society of the District of Columbia
*Secretary*, Dr. William E. Sheely, 1746 K St., N.W., Washington 6, D. C. Meets at Medical Society Library, third Wednesday of January, March, May and October at 8:00 P.M.

Section on Radiology, Illinois State Medical Society
*Secretary*, Dr. William Meszaros, 1825 W. Harrison St., Chicago, Ill.

Section on Radiology, Southern Medical Association.
*Secretary*. Dr. Seymour Ochsner, Ochsner Clinic, 3503 Prytania St., New Orleans 15, La. Annual meeting to be announced.

Shreveport Radiological Club
*Secretary*, W. R. Harwell, 608 Travis St., Shreveport, La. Meets monthly on third Wednesday, at 7:30 P.M., September to May inclusive.

Society for Pediatric Radiology
*Secretary*, Dr. Richard G. Lester, 412 Union St., S.E., Minneapolis 14, Minn. Annual meeting: Deaville Hotel, Miami Beach, Fla., Sept. 25, 1961.

Society of Nuclear Medicine
*Secretary*, Dr. Robert W. Lackey, 452 Metropolitan Bldg., Denver 2, Colo. *Administrator*, Samuel N. Turiel, 430 N. Michigan Ave., Chicago 11, Ill. Annual meeting: Penn Sheraton Hotel, Pittsburgh, Pa., June 14–17, 1961.

South Bay Radiological Society
*Secretary*, Dr. Stanford B. Rossiter, 1111 University Dr., Menlo Park, Calif. Meets second Wednesday of each month.

South Carolina Radiological Society
*Secretary*, Dr. George W. Brunson, 1406 Gregg St., Columbia, S. C. Annual meeting (primarily business) in conjunction with the South Carolina Medical Association meeting in May. Annual fall scientific meeting at time and place designated by the president.

Southern Radiological Conference
*Secretary*, Dr. Marshall Eskridge, Mobile Infirmary Mobile, Ala.

Southwestern Radiological Society
*Secretary*, Dr. Ralph S. Clayton, 1501 Arizona, Bldg. 2-A, El Paso, Texas. Meets second Tuesday of each month.

Tennessee Radiological Society
*Secretary*, Dr. James J. Range, P.O. Box 324, Johnson City, Tenn. Meets annually at the time and place of the Tennessee State Medical Association meeting.

Texas Radiological Society
*Secretary*, Dr. R. P. O'Bannon, 402 Professional Bldg., 1216 Pennsylvania Ave., Fort Worth 4, Texas. Next meeting January 20 and 21, 1961, Texas Hotel, Fort Worth, Texas.

Tri-State Radiological Society
*Secretary*, Dr. James R. Mathews, 118 S. E. First St., Evansville, Ind. Meets last Wednesday of Oct., Jan., March and May, 8:00 P.M. at Elks' Club in Evansville.

University of Michigan Department of Roentgenology Staff Meeting
Meets each Monday evening from September to June, at 7:00 P.M. at University Hospital.

Upper Peninsula Radiological Society
*Secretary*, Dr. A. Gonty, Menominee, Mich. Meets quarterly.

Utah State Radiological Society
*Secretary*, Dr. Richard Y. Card, St. Mark's Hospital, Salt Lake City, Utah. Meets fourth Wednesday in January, March, May, September and November at Holy Cross Hospital.

Virginia Radiological Society
*Secretary*, Dr. Powell G. Dillard, Jr., 715 Church Street, Lynchburg, Va. Meets annually in October.

Washington State Radiological Society
*Secretary*, Dr. Joseph T. Houk, 14303 Ambaum Blvd., Seattle 66, Wash. Meets third Monday of each month from September through April at the University of Washington Medical School.

West Virginia Radiological Society
*Secretary*, Dr. Karl J. Myers, 112 N. Woods St., Philippi, W. Va. Meets concurrently with Annual Meeting of West Virginia State Medical Society; other meetings arranged by program committee.

Westchester Radiological Society
*Secretary*, Dr. Richard P. Avondu, Yonkers General Hospital, Park & Ashburton Ave., Yonkers, N. Y. Meets on third Tuesday of January and October and on two other dates.

Wisconsin Radiological Society
*Secretary*, Dr. Howard G. Bayley, 116 Iroquois Parkway, Beaver Dam, Wis. Annual meeting each spring in various places.

X-Ray Study Club of San Francisco
*Secretary*, Dr. John H. Heald, 450 Sutter St., San Francisco 8, Calif. Meets monthly, third Thursday at 7:30 P.M., Children's Hospital, September through June.

### Cuba, Mexico, Puerto Rico and Central America

Asociación de Radiólogos de Centro America y Panamá. Comprising: Guatemala, El Salvador, Honduras, Nicaragua, Costa Rica and Panamá.
*Secretary-General*, Dr. Julio Toriello, 11 Calle 2-37, zona 1, Guatemala. Meets annually in a rotating manner in the six countries.

Sociedad de Radiología de El Salvador
*Secretary*, Dr. Rafael Vega Gómez.

Sociedad de Radiología de Guatemala
*Secretary*, Dr. Carlos E. Escobar, 9ª. Calle A 0-05, Zona 1, Guatemala.

Sociedad de Radiología y Fisioterapía Cubana
*Secretary*, Dr. Miguel A. García Plasencia, Hospital Curie, 29 y F, Vedado, Habana, Cuba. Meets monthly at Curie Hospital.

Sociedad Costarricense de Radiologia
*Secretary*, Dr. James Fernández Carballo, Apartado VIII, San José, Costa Rica.

Sociedad Mexicana de Radiología, A. C.
Calle del Oro No. 15, México 7, D. F.
*Secretary-General*, Dr. E. Alvarez Hernández. Meets first Monday of each month.

Asociación Puertorriqueña de Radiología
*Secretary*, Dr. R. B. Díaz Bonnet, Suite 504, Professional Bldg., Santurce, Puerto Rico.

Sociedad Radiológica Panameña
*Secretary*, Dr. L. Arrieta Sánchez, Apartado No. 6323, Panamá, R. de P. Meets monthly in a department of radiology of a local hospital, chosen at preceding meeting.

Sociedad Radiológica de Puerto Rico
*Secretary*, Dr. César E. Rosa-Perez, Fondo del Segura del Estado, Parada 1, San Juan 8, Puerto Rico. Meets second Thursday of each month at 8:00 P.M. at the Puerto Rico Medical Association Bldg. in San Juan.

### British Commonwealth of Nations

Association of Radiologists of the Province of Quebec
*Secretary*, Dr. Odilon Raymond, 5400 Blvd. Gouin. Quest, Montreal, Que. Meets four times a year.

British Institute of Radiology Incorporated with the Röntgen Society
*Honorary Secretary*, Dr. John Blewett, 32 Welbeck St., London, W. 1. Meets monthly from October until May.

Faculty of Radiologists
*Honorary Secretary*, Dr. R. A. Kemp Harper, 47 Lincoln's Inn Fields, London, W.C.2, England. Annual meeting to be announced.

Section of Radiology of the Royal Society of Medicine ((Confined to Medical Members),
Meets third Friday each month at 4:45 P.M. at the Royal Society of Medicine, 1 Wimpole St., London, W. 1.

Canadian Association of Radiologists
*Honorary Secretary*, Dr. Robert G. Fraser, *Associate Honorary Secretary*, Dr. Jean-Louis Léger, 1555 Summerhill Ave., Montreal 25, Que. Annual meeting to be announced.

Montreal Radiological Study Club
*Secretary*, Dr. F. McConnell, 1650 Cedar Ave., Montreal, Quebec. Meets first Tuesday evening, October to April.

Section of Radiology, Canadian Medical Association
*Secretary*, Dr. C. M. Jones, Inglis St., Ext. Halifax, N. S.

Société Canadienne-Française d'Electro-Radiologie Médicale
*General Secretary*, Dr. Louis Ivan Vallée, 1058 rue St-Denis, Montreal 18, Canada. Meets third Saturday each month.

Toronto Radiological Society
*Secretary*, Dr. L. R. Harnick, Toronto Western Hospital, 399 Bathurst St., Toronto, Ontario. Meets second Monday of each month September through May.

College of Radiologists of Australasia
*Honorary Secretary*, Dr. E. A. Booth, c/o British Medical Agency, 135 Macquarie St., Sydney, N.S.W., Australia.

### South America

Asociación Argentina de Radiología
*Secretary*, Dr. Lidio G. Mosca, Avda. Gral. Paz 151, Córdoba, Argentina. Meetings held monthly.

Ateneo de Radiologia
*Secretary*, Dr. Victor A. Añaños, Instituto de Radiologia, Santa Fe 3100, Rosario, Argentina. Meets monthly on second and fourth Fridays at 7:00 P.M. in the Hospital Nacional del Centenario, Santa Fe 1300, Rosario.

Colégio Brasileiro de Radiologia
*Secretary-General*, D. Camillo Segreto, Avenida Angélica, 1.170, Caixa Postal 5984, São, Paulo, Brazil.

Sociedad Argentina de Radiología, Junta Central Buenos Aires
*Secretary*, Dr. Edgardo O. Olcese, Santa Fé 1171, Buenos Aires. Meetings are held monthly.

Sociedad Bolivana de Radiología
*Secretary*, Dr. Javier Prada Méndez, Casilla 1596, La Paz, Bolivia. Meets monthly. General assembly once every two years.

Sociedade Brasileira de Radiologia
*Secretary*, Dr. Nicola Caminha, Av. Mem. de Sa, Rio de Janeiro, Brazil. General Assembly meets every two years in December.

Sociedade Brasileira de Radioterapia
*Secretary*, Dr. Oscar Rocha von Pfuhl, Av. Brigadeiro Luiz Antonio, 644 São Paulo, Brazil. Meets monthly on second Wednesday at 9:00 P.M. in São Paulo at Av. Brigadeiro Luiz Antonio, 644.

Sociedad Chilena de Radiología
*Secretary*, Dr. J. P. Velasco, Avenida Santa María 0410, Santiago, Chile. Meets fourth Friday of each month.

Sociedad Colombiana de Radiologia
*Secretary*, Dr. Alberto Mejía Diazgranados, Carrera 13, No. 25–31, Apartado aéreo No. 5804, Bogotá, Colombia. Meets last Thursday of each month.

Sociedad Ecuatoriana de Radiología y Fisioterapía
*Secretary*, Dr. Publio Vargas P., Casilla 1242, Guayaquil, Ecuador.

Sociedad Paraguaya de Radiología
*Secretary*, Dr. Miguel González Addone, 15 de Agosto 322, Asunción, Paraguay.

Sociedad Peruana de Radiologia
*Secretary*, Dr. Luis Pinillos Ganoza, Apartado 2306, Lima, Perú. Meets monthly except during January, February and March, at Asociación Médica Peruana "Daniel A. Carrión," Villalta 218, Lima.

Sociedad de Radiologia del Atlantico
*Secretary*, Dr. Raul Fernandez, Calle 40 #41-110, Baranquilla, Colombia. Society meets monthly at the Instituto de Radiologia.

Sociedad de Radiología, Cancerología y Física Médica del Uruguay
*Secretary-General*, Dr. Ernesto H. Cibils, Av. Agraciada 1464, piso 13, Montevideo, Uruguay.

Sociedade de Radiologia de Pernambuco
*Secretary*, Dr. Manoel Medeiros, Instituto de Radiologia da Faculdade de Medicina da Universidade do Recife, Caixa Postal 505, Pernambuco, Brazil.

Sociedad de Roentgenologia y Medicina Nuclear de la Provincia de Córdoba
*Secretary-General*, Dr. Carlos A. Oulton, Santa Rosa 447, Córdoba, Argentina.

Sociedad Venezolana de Radiología
*Secretary-General*, Dr. Rubén Merenfeld, Apartado No. 9362, Candelaria, Caracas, Venezuela. Meets monthly third Friday at Colegio Médico del Distrito Federal, Caracas.

### Continental Europe

Österreichische Röntgen-Gesellschaft
*President*, Dr. Konrad Weiss, Mariannengasse 10, Vienna 9, Austria. Meets second Tuesday of each month in Allgemeine Poliklinik.

Société Belge de Radiologie
*General Secretary*, Dr. S. Masy, 256 Chaussée de Wavre, Heverlee-lez-Louvain, Belgium. Meets in February, March, May, June, October, November and December.

Société Française d'Electroradiologie Médicale, and its branches: Société du Sud-Ouest, du Littoral Méditerranéen, du Centre et du Lyonnais, du Nord, de l'Ouest, de l'Est, et d'Alger et d'Afrique du Nord. Central Society meets third Monday of each month, except during July, August and September, rue de Seine 12, Paris.
*Secretary-General*, Dr. Ch. Proux, 9, rue Daru, Paris 8e, France.

Československá Společnost pro Roentgenologii a Radiologii
*Secretary*, Dr. Robert Poch, Praha 12, Šrobárova 50, Czechoslovakia. Meets monthly except during July, August, and September. Annual general meeting.

Deutsche Röntgengesellschaft
*Secretary*, Professor Dr. med. H. Lossen, Universitäts-Röntgeninstitut. Lagenbeckstr. 1, Mainz, Germany. Annual meeting: April 16–19, 1961, in Hamburg.

Società Italiana di Radiologia Medica e di Medicina Nucleare
*Secretary*, Dr. Ettore Conte, Ospedale Mauriziano, Torino, Italy. Meets annually.

Nederlandse Vereniging voor Electrologie en Röntgenologie
*Secretary*, Dr. J. R. von Ronnen, Violenweg 14, den Haag Netherlands.

Scandinavian Roentgen Societies
The Scandinavian roentgen societies have formed a joint association called the Northern Association for Medical Radiology, meeting every second year in the different countries belonging to the Association.

Sociedad Española de Radiología y Electrología Médicas y Medicina Nuclear
*Secretary*, Dr. D. Aureo Gutierrez Churruca, Esparteros, No. 9, Madrid, Spain. Meets monthly in Madrid.

Schweizerische Gesellschaft für Radiologie und Nuklearmedizin (Société Suisse de Radiologie et de Médecine Nucléaire)
*Secretary*, Dr. Max Hopf, Effingerstrasse 47, Bern, Switzerland.

### India

Indian Radiological Association
*Secretary*, Dr. R. F. Sethna, Navsari Building, Hornby Road, Bombay 1, India.

The next list of Meetings of Radiological Societies will be published in the May, 1961 issue of the Journal.

# ABSTRACTS OF RADIOLOGICAL LITERATURE

*Department Editor:* T. Leucutia, M.D., Harper Hospital, Detroit 1, Michigan

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## ROENTGEN DIAGNOSIS

### Head

Feinberg, S. B. Congenital mesodermal dysmorpho-dystrophy (brachymorphic type). *Radiology*, Feb., 1960, *74*, 218–224. (Address: 737 E. 22nd St., Minneapolis 4, Minn.)

Dysmorpho-dystrophia mesodermalis congenita, or congenital mesodermal dystrophy, appears to be a suitable broad category in which to include the findings described by Marfan at one extreme (*i.e.*, the hypoplastic, arachnodactylic, or dolichomorphic type) and Marchesani at the other (*i.e.*, the hyperplastic, brachydactylic, or brachymorphic type). Marchesani's syndrome *per se* has not been reported in either the American or foreign radiologic literature, although it has been described in the publications in other fields. The syndrome includes short stature, a brachycephalic skull, brachydactyly, well-developed subcutaneous tissues, myopia and glaucoma with frequent association of spherical and/or dislocated lenses, and sometimes congenital heart defects. A familial tendency and consanguinity in the parents have been reported.

Roentgenologically, the skull, facial bones, hands, and feet have been the primary areas of involvement. The most obvious finding is grotesque exaggeration of brachycephaly, with small, shallow, closely placed orbits, diminutive maxillae, hypoplastic zygomatic arches, arched palate, and either actually or relatively prognathic mandible. The presence of depressed maxilla and prognathic mandible set this syndrome apart from craniofacial mandibular dysostosis.

Two cases are presented, occurring in sisters aged ten and seven at the time of admission, with similar findings in each child. There was a history of retarded development, repeated respiratory infections, poor vision associated with headaches, fatigability, and recurrent ulcerations of the feet. Heart murmurs were discovered in each child in infancy. Each was noted to have a prominent forehead with abundant coarse hair extending low on the forehead and neck, hypoplastic maxillae with a high arched palate and maldeveloped, deformed, and misdirected teeth. The mandible appeared prognathic. There were small sunken eyes with lids which could not completely open and reversed lid angles. There was poor vision associated with abnormalities of the ocular structures. The hands and feet were short and broad, as well as thick. The skin folds, especially about the hands and thighs, were thickened, and the hands showed ulnar deviation. There was clinical and roentgenologic evidence of patent ductus arteriosus, which was corrected surgically in each child. Roentgenographic findings included the strikingly brachycephalic skull, with shallow, hypoplastic, asymmetric orbits, hypoplastic and depressed maxillae, maldeveloped teeth, and relatively prognathic mandible. The metacarpals, metatarsals, and phalanges were short and broad, and one child had roentgen evidence of retarded bone age. The long bones were somewhat short but not broad.—*Walter H. Jarvis, Jr., M.D.*

### Genitourinary System

Hildreth, Eugene A., Pendergrass, Henry P., Tondreau, Roderick L., and Ritchie, David J. Reactions associated with intravenous urography: discussion of mechanisms and therapy. *Radiology*, Feb., 1960, *74*, 246–254. (Address: E. A. Hildreth, Hospital of the University of Pennsylvania, Philadelphia 4, Pa.)

The use of iodide compounds for intravenous urography is increasing rapidly. In the United States alone there has been a fivefold increase in the past fourteen years and, as a result, more fatal as well as nonfatal reactions are being reported each year. The clinical picture of reactions associated with intravenous urography is that of a mild toxic reaction or an allergic reaction. The mild toxic reactions consist of phlebitis, pain in the arms, nausea, flushing, giddiness, tingling, numbness, and cough. These seldom proceed to more serious consequences. The allergic reactions may be mild (urticaria, conjunctivitis or rhinitis) or severe (dyspnea, shock, or cyanosis). These allergic reactions are the ones that endanger life.

The exact mechanism of the reactions to organic contrast media is not clear but at least three possible causes have been considered: toxicity, pharmacologic idiosyncrasy, and allergy. Neither pharmacologic idiosyncrasy nor toxicity can be implicated seriously. The exceptions, where toxicity was a major factor, have been observed chiefly in children receiving large doses and in patients otherwise seriously ill. The available evidence indicates that allergy is the chief cause of serious and fatal reactions.

At present reactions to the iodides cannot be predicted accurately. A history of allergy can be used as a warning but is not of itself an absolute contraindication. Also, as the authors state, "the immediate wheal and erythema skin tests (reagenic type) are worthless in predicting reactions to the iodides now being used in contrast study." Therefore, it is suggested that the most practical approach is to test the patient by observing his tolerance for a small dose of the medium. An experimental program is presented that may be of value or may lead to new techniques in preventing reactions. This consists of a careful history, prior subcutaneous testing with dilute contrast material, a small test dose at the time of examination, and careful observation for reactions following the injection.

When reactions occur they can immediately assume the most serious proportions. Therefore, the

first step in therapy is the establishment of an emergency plan of action. If allergic manifestations appear, therapy proceeds according to the type of reaction. The reactions of dyspnea wheezing or cyanosis are immediately treated with epinephrine (intramuscularly administered epinephrine HCl, 1:1000, 0.5 cc.) with concurrent attention to proper oxygenation and establishment of an airway if cyanosis appears. If shock appears, longer acting vasopressors are used. It is emphasized that convulsions are most often associated with cyanosis and are due to anoxia. Barbiturates are helpful in convulsions not due to anoxia but they would be harmful in the presence of cyanosis.

For the reactions of asthma and pulmonary edema, epinephrine is recommended although aminophylline and prednisolone 21-phosphate are valuable. In the event of total vascular collapse and coma, the authors recommend epinephrine, the shock position, vasopressors, oxygen and prednisolone 21-phosphate. Laryngeal edema is rare but is best treated with epinephrine with or without tracheotomy. Cortisone-like drugs are not useful in the first critical minutes and respiratory stimulants and calcium therapy have no value. In the event of cardiac arrest, the authors suggest the simpler methods of cardiac resuscitation such as blows to the chest, cardiac stimulation by injections, and rocking the patients knees against his chest.—*Edward B. Best, M.D.*

## Skeletal System

McGavran, M. H., and Spady, H. A. Eosinophilic granuloma of bone; a study of twenty-eight cases. *J. Bone & Joint Surg.*, Sept., 1960, *42-A*, 979–992. (From: Division of Surgical Pathology and Orthopaedic Surgery, Department of Surgery, Washington University School of Medicine, Barnes Hospital, St. Louis Children's Hospital, and the Barnard Free Skin and Cancer Hospital, St. Louis, Mo.)

This is a review of 28 proved cases of eosinophilic granuloma of bone. All but 1 were symptomatically single. Clinical observations must be considered in arriving at a diagnosis and patients with dermatitis, lymphadenopathy, hepatosplenomegaly, anemia, thrombopenia, otitis media, diarrhea, diabetes insipidus or pulmonic infiltration were classified as either Abt-Letterer-Siwe disease or Hand-Schüller-Christian syndrome.

There were 15 male and 13 female patients with an average age of 13.3 years. Only one patient was over 30. The common sites of the lesions were the skull and femur, each with 7 lesions and the ribs and mandible with 3. Pain of short duration was the presenting symptom. The laboratory studies were not of diagnostic assistance. In 1 case out of 9 in which bacterial cultures were done, the authors isolated an atypical acid fast organism on culture but were unable to determine its significance.

Roentgenologically, the lesions in the flat bones appeared as sharply defined, "punched-out" areas. None had button sequestra. A dermoid cyst may have a similar appearance. The rib lesions were lobulated, destructive and expansile with slight periosteal reaction. In the long bones there was no involvement of the epiphyses. In children the lesions may be difficult to differentiate from Ewing's tumor or osteomyelitis, since they are a destructive process with erosion of the cortex and moderate to marked new bone formation with periosteal layering. In adults the lesions in the long bones showed as ill defined central radiolucencies with little cortical erosion or periosteal reaction.

No plan of therapy was followed routinely. The skull and rib lesions were usually excised. The other lesions were not treated or had curettage or irradiation.

Serial roentgenograms were available in only 9 cases, but in all 28 no signs or symptoms persisted after treatment. In 1 case a soft tissue implant developed in the scar after biopsy and irradiation. There were no cases with transition to Hand-Schüller-Christian disease.

The authors urge careful microbiologic study of the tissues removed at surgery to better clarify the etiology of these lesions.—*Martha Mottram, M.D.*

Aakhus, Trygve, Oddvan, Eide, and Stokke, Trovald. Parosteal osteogenic sarcoma. *Acta radiol.*, July, 1960, *54*, 29–40. (From: The General Department and the Pathology Laboratory, The Norwegian Radium Hospital, Oslo, Norway.)

The authors present their experiences with 5 cases of parosteal osteogenic sarcoma selected from their 85 cases of osteogenic sarcoma over a fifteen year period, and briefly review the literature. Their findings were essentially the same as reported previously.

Thirty-four previous cases have been reported. There is no sex predominance. The average age is higher than in cases of osteogenic sarcoma with 44 per cent being over thirty years of age. Duration of symptoms is prolonged. The tumor is usually metaphyseal with the distal femur being the most common location.

The roentgenologic appearance is described as a juxtacortical, broad-based, densely ossified mass. Sclerosis is most marked at the base with an irregular periphery. Rarefactions may be present within the tumor. Characteristically, the tumor encircles the shaft with cortical thickening at the point of attachment. The usual signs of malignancy are absent. The appearance may remain unchanged for years. Recurrence after inadequate excision may appear in the surrounding soft tissues.

The histologic appearance of the tumor is characteristic in typical cases. However, findings will vary from one area of the lesion to another, often causing under-rating of the tumor by the pathologists.

Of the 39 patients, 8 died after an average of eight years. One of these was treated by irradiation; the others by surgery. Twenty-one are alive after an average of seven years. Sixteen had primary excisions; the others amputations. Ten died of other causes, or the information obtained was unreliable. The authors feel that radiation therapy is of little avail. Permanent cure can be expected only after wide excision. Recurrence is common after local excision with the recurrent tumor being more highly malignant. Ultimately, extensive metastases are found. These often are slow growing.

Similar lesions are briefly discussed. Myositis ossificans and ossifying subperiosteal hematomas usually have a preceding history of trauma. These also tend to reach a maximum size and then regress. An osteochondroma usually does not encircle the shaft and has a core of cancellous tissue continuous with the medulla. Sclerotic osteogenic sarcoma is rapidly growing, has the characteristics of malignancy, and is usually associated with systemic reactions.—*Barry Gerald, M.D.*

Aitken, A. P., and Nalebuff, E. A. Volar transnavicular perilunar dislocation of the carpus. *J. Bone & Joint Surg.*, Sept., 1960, *42-A*, 1051–1057. (From: Orthopaedic Service, Boston City Hospital, Boston, Mass.)

The usual perilunar dislocation is of the dorsal type with a transnavicular fracture.

A case is presented of a twenty-one year old male who fell and landed on the dorsum of the flexed hand, sustaining a volar perilunar dislocation with fracture of the navicular. The larger distal navicular fragment was displaced anteriorly while the other carpal bones and the smaller proximal fragment remained with the lunate. Reduction was easily obtained with traction. The position could be maintained in moderate extension. The hand was immobilized for ten weeks. The navicular showed nonunion. There was aseptic necrosis of the lunate at fourteen months, but at two and one-half years this had revascularized.

In falls on the extended hand either an anterior dislocation of the lunate or a retrolunar dislocation of the other carpal bones may be produced, depending on the degree of extension and direction of force. In falls on the flexed hand, there may be an extremely rare dorsal dislocation of the lunate or a volar perilunar dislocation of the carpal bones. These latter lesions are uncommon due to the natural tendency to extend the hand in a fall.

The prognosis in perilunar dislocation is guarded, particularly when associated with fracture of the navicular. Aseptic necrosis will occur in 50 per cent or more of the fractures.—*Martha Mottram, M.D.*

Packer, James M., Harris, Elmer J., and Henderson, Robert P. Bilateral synostosis of seventh rib and scapula; a case report. *Radiology*, Feb., 1960, *74*, 289–290. (Address: J. M. Packer, 1190 North State St., Jackson 2, Miss.)

The authors report a single case of bilateral, symmetric, congenital synostosis between the seventh posterior ribs and the inferior angles of the scapulae. This proved to be an isolated skeletal anomaly in a patient who had led an active life with no significant disability except for restriction of all motion of the shoulder and upper extremity involving scapular movement. This was the first time the authors had observed this type of anomaly and they were unable to discover in the literature published in the past ten years any article referring to this particular abnormality. There are many other commonly encountered types of rib abnormalities reported such as bifid anterior, hypoplastic and hyperplastic cervical ribs, and the group of synostoses and pseudoarthroses between adjoining ribs.—*W. M. McBride, M.D.*

Brou, M. (Luluabourg, Congo). Syndrome de Klippel-Feil chez un enfant Congolais. (The Klippel-Feil syndrome in a Congolese infant.) *J. belge de radiol.*, Mar., 1960, *43*, 221–226.

The authors report a case of a Klippel-Feil syndrome in a nine year old Congolese child, who was admitted with a diagnosis of Pott's disease. The child was of medium height with a moderately pronounced dorsolumbar kyphosis. There was a cervicodorsal scoliosis with convexity to the left in the lower half of the spine, with a reverse curvature in the upper half of the cervical spine and decreased mobility of the neck. Except for the obvious skeletal deformity, there were no abnormalities on physical examination. Laboratory tests were not contributory.

The distinguishing feature in the history was the fact that the deformity had not changed in appearance or degree since birth. This was considered, from a clinical point of view, as an argument against the diagnosis of Pott's disease.

The striking roentgen findings were fusion of the atlas and the axis, the butterfly appearance of $C_3$ and $C_4$ with dehiscence of the central portion of the bodies, congenital absence of C6 and $C_7$, hemivertebra of $D_1$ with agenesis of the left half and hemivertebra of $D_2$ with agenesis of the right half, the butterfly appearance of $D_3$ caused by incomplete fusion of the two lateral masses of the body, and a normal $D_4$ with fusion of the bodies of the first four dorsal vertebrae but with adequate delineation of the

contour of each individual body being maintained. There were no abnormalities from D5 to D12. There was a cuneiform aspect of L1 and L2, as seen in the lateral projection, due to agenesis of the anterior halves with fusion of the bodies. There was no abnormality of the vertebrae below this point.

There was incomplete fusion of the first five right ribs. The right sixth rib was rather well defined but it was partially fused to the one immediately above. The two first left ribs were partially fused. The remaining ribs were not remarkable.

This is the first such case reported from the Congo and apparently is significant to the author because of the high incidence of Pott's disease in that area.—*William H. Shehadi, M.D.*

### Blood and Lymph System

Puijlaert, C. B. A. J. Biphasic serial aorto-arteriography; (principles, method and apparatus). *J. belge de radiol.*, Mar., 1960, *43*, 261–274. (From: Radiological Department of St. Elizabeth Hospital, Tilburg, Holland.)

A method of adequately and simultaneously visualizing the circulation from the level of the distal aorta inferiorly to include both lower extremities is described. Angiograms are taken throughout the arterial and venous phases of the circulation. The necessity of visualizing such a large area lies in the fact that the location of pathology may be extensive and the rate of circulation in the two lower extremities may vary considerably depending upon the pathology present in one or the other.

The basis of this method is two injections made into the aorta through the same needle with an interval of approximately one minute. Manual exposures of the lower extremity are made after the first injection, followed by rapid semi-automatic exposures of the faster pelvic circulation after the second injection.

This method has a distinct advantage in that areas requiring different exposure times do not have to be visualized in one roentgenogram, thus avoiding needless exposure of either the extremities or the pelvis.

The simple apparatus consists essentially of a carrier for the two sets of films which is placed beneath the patient and is moveable in order to give some degree of overlapping.—*Everett G. Davis, Jr., M.D.*

Graumann, Walter. Methodik und Bedeutung der Splenoportographie. (Procedure and importance of splenoportography.) *Röntgen Blätter*, Sept., 1960, *13*, 257–271. (Address: Strahlenabteilung Augusta-Viktoria-Krankenhaus, Canovastr. 9, Berlin-Friedenau, Germany.)

Liver angiography can be performed in one of three ways: (1) by injecting contrast material directly into the hepatic artery, (2) by catheterizing three hepatic veins via the inferior vena cava (coincidental filling may occur during angiocardiography in tricuspid atresia), and (3) by injecting the medium into the spleen (splenoportography).

Whenever an injection into the spleen is performed, there is the small but definite risk of rupture of the splenic capsule, which could result in fatal hemorrhage. Therefore, splenic puncture should be done only in an institution in which facilities for immediate splenectomy are available. For the same reason it is preferable to puncture the spleen during general anesthesia with intubation; under bag-breathing, apnea may be induced for the roentgen exposures, and shallow respiratory movements during the time when the needle is actually in the spleen will minimize the risk of trauma to the splenic capsule.

It is farily simple to insert a needle into a large spleen but, when the spleen is of the usual size or smaller, it may be quite difficult to find the organ and to make the injection as close as possible to the splenic hilum so as to insure easy flow of the contrast material. The author prefers first to execute laparoscopy (peritoneoscopy) under general intubation anesthesia and, if he still needs more information, he will insert the needle into the spleen under endoscopic control.

After the needle has been placed, it is important to measure the pressure, which is done by attaching a U-shaped manometer. This necessitates keeping the needle in the spleen a few minutes longer than otherwise, but this measurement is sufficiently important to justify the additional, small risk. Then 30–55 cc. of contrast material is injected in 4–5 seconds. The entire procedure is performed with the patient on a roentgenographic table provided, if possible, with a seriograph.

The author uses a triphasic 1,000 ma.transformer and a tube-skin distance of 110 cm. with 88–92 kv. and 30–40 mas. (0.12–0.16 sec.). For the first ten seconds after the injection, one frame is exposed every second, then additional views are taken at 20, 30, and 40 seconds.

After termination of the procedure, the patient should rest for about four hours in the left lateral decubitus position. He should be kept under strict (preferably hospital) observation for seven days thereafter, because delayed hemorrhage is known to have occurred.

The actual puncture of the spleen is performed with a 12 cm. needle inserted through the ninth or tenth intercostal space, between the anterior and midaxillary line. If there is enlargement of the spleen, the puncture should be performed below the costal margin. When the spleen is smaller than normal, the patient may be placed in the prone position.

The value of splenoportography is to demonstrate the existence of portal hypertension, and to help the

surgeon decide which by-pass intervention has the better chance of success. The delay in portal circulation may be: (a) in the liver itself (cirrhosis, tumor); (b) prehepatic (portal or splenic thrombosis, tumors or inflammations of the pancreas, enlarged mesenteric lymph nodes); or (c) posthepatic (severe cardiac decompensation with right heart stasis).

In cirrhosis, the large ramifications of the portal vein are well filled, but not the smaller ones. In the next stage, because of stasis, the splenic vein becomes tortuous and collateral circulation then develops through the dilated (varicose) esophageal veins. In cases of tumors, vessels may be displaced by extrinsic masses or, as in the case of retothel-sarcoma of the spleen, newly formed (increased) vascular supply to the tumor may become visible.—*E. R. N. Grigg, M. D.*

Marcozzi, G., Messinetti, S., Colombati, M., and Mocavero, G. La visualizzazione del sistema azigos mediante flebografia vertebrale transomatica. (The visualization of the azygos system using trans-somatic vertebral phlebography.) *Ann. ital. di chir.*, Apr., 1960, *37*, 265–283. (From: Istituto di Clinica Chirurgica Generale e Terapia Chirurgica della Università, Perugia, Italy.)

The authors, after reviewing methods for visualizing the azygos vein by mediastinal laminagraphy and by intraosseous, costal-intraosseous and intraspinous venographic techniques, describe a personal technique that they name "trans-somatic vertebral phlebography."

The patient is placed on the fluoroscopic table in the prone position. A radiopaque landmark is placed on the spinous process of the first or second lumbar vertebra. A special needle designed by the authors (not described or illustrated in the text) is then inserted below the left twelfth rib on the external margin of the longissimus dorsi muscle. The needle, under fluoroscopic control, is directed dorsoventrally and to the right toward the midpoint of the left body surface of L2. In order to reach the body of L1, the needle has to be directed cephalad also.

The puncture of L1 is preferable for elective visualization of the entire azygos vein. The puncture of L2 is recommended for also visualizing the spinal and intercostal veins, which are tributaries of the azygos vein.

Before puncturing the vertebral body, the exact position of the needle tip is determined by a lateral roentgenogram taken with the patient in the prone position. The needle is then pushed by gentle screwing movements into the spongy center of the vertebral body from which blood can be easily aspirated and replaced by slight movements of the syringe plunger. The position of the needle is checked again by posteroanterior and lateral roentgenograms.

At this point, 40 or 50 cc. of angiombrine (Dagra) —which contains 74 per cent iodine and is very fluid —is injected in five or six seconds by a common syringe which is connected to the needle by a polyethylene tube. The best visualization of the azygos vein occurs immediately after the end of the injection. Ten seconds later the left heart cavities are filled and at the eleventh second the thoracic aortogram can be made.

The inferior vena cava also is opacified because the medium refluxes into the vertebral and lumbar veins which are below the injected vertebra and from there passes into the inferior vena cava.

The authors applied this technique in studying mediastinal tumors, superior caval obstruction and portal hypertension syndromes.—*Frank L. Campeti, M. D.*

Di Matteo, G., and Morabito, A. Rilievi anatomo-funzionali sul circolo linfatico nell' arto superiore mediante linfangioadenografia; considerazioni sui fondamenti etiopatogenetici dell'edema indurativo postmastectomia. (Anatomicophysiologic study of the lymphatic system of the superior extremity using lymphangioadenography; consideration of the fundamental etiopathology of postmastectomy indurative edema.) *Ann. ital. di chir.*, May, 1960, *37*, 363–383. (From: Istituto di Clinica Chirurgica dell'Università, Perugia, Italy.)

The authors, after two years of experience with lymphoadenoangiography of the superior extremity, present interesting observations on the morphology and function of the lymphatic system of this area.

The unsettled problem of the hard edema which sometimes follows mastectomy associated with the removal of the axillary lymph nodes is extensively discussed.—*Frank L. Campeti, M. D.*

Di Matteo, G., and Morabito, A. Ricerche sull'anatomia funzionale radiologica del sistema linfatico soprafasciale degli arti in corso di flebopatie infiammatorie e dinamiche. (Radiologic study of the anatomy and function of the suprafascial lymphatic system of the extremities in the course of inflammatory and dynamic phlebopathies.) *Ann. ital. di chir.*, Apr., 1960, *37*, 284–294. (From: Istituto di Clinica Chirurgica dell'Università, Perugia, Italy.)

The authors studied the lymphatic system of the lower extremities in 30 patients affected by thrombophlebitis, venous thrombosis and venous varices. They used the lymphangioadenographic technique according to J. B. Kinmoth *et al.* (*Brit. M. J.*, 1955, *4*, 940) and demonstrated in the majority of their

cases that morphologic and functional alterations of the lymphatic system are concomitant with the venopathies and their functional sequelae. These abnormalities of the lymphatic system are, according to the authors, an important etiologic factor in syndromes of vascular insufficiency, generally considered to be due to primary venous lesions.—*Frank L. Campeti, M. D.*

Lippmann, Heinz I., and Goldin, Ralph R. Subcutaneous ossification of the legs in chronic venous insufficiency. *Radiology*, Feb., 1960, *74*, 279–288. (Address: H. I. Lippmann, 1710 Newport Ave., New York 61, N. Y.)

The authors report a series of 60 cases in which subcutaneous ossification of the legs was present. In all of these patients this ossification occurred as a late complication of chronic venous insufficiency with the typical clinical manifestations of a chronic dermatitis and cellulitis, and atrophy of the skin and subcutaneous tissue with induration and brown discoloration being present. The condition was unilateral in 33 and bilateral in 27, giving a total of 87 legs which were evaluated in this study. All patients were females past the menopause, and 57 (95 per cent) had obesity.

The ossification was clearly established to be located in the subcutaneous tissues by means of roentgenograms using soft tissue techniques, venography and, in some instances, laminagraphic studies. In 6 cases there was pathologic confirmation from biopsy specimens obtained during surgical treatment for some complication. The roentgenographic appearance of the ossifications varied according to the amount and extent of involvement. Some showed fine granular densities. Others showed delicate oval or cylindrical densities which often interlaced and coalesced. Frequently these densities demonstrated thin rims and lucent centers which sometimes had a fine web-like pattern. Heavy cords and sheets which retained central lucent zones and trabeculation were also demonstrated in several instances.

The differential diagnosis includes: phleboliths, arterial calcifications, myositis ossificans, calcification of infestations, periarticular ossification associated with disease of the spinal cord, various forms of calcinosis, calcification within localized areas of trauma and necrosis, and Ehlers-Danlos syndrome. Careful evaluation of the calcific densities correlated with the clinical picture will in most cases lead to the proper diagnosis.

Pathologically, the heterotropic tissue consisted of cancellous bone in plates or rings, in the center of which were fat cells. No cartilaginous tissue was encountered and no ossification was found within the lumen or wall of the vein. The pathogenesis of this subcutaneous ossification is being studied but as yet no disturbance in systemic calcium and phosphorus metabolism has been found.—*Donald N. Dysart, M.D.*

## RADIATION THERAPY

Frick, Henry Clay, II, Taylor, Howard C., Jr., Guttmann, Ruth J., Jacox, Harold W., and McKelway, William P. A study of complications in the surgical and radiation therapy of cancer of the cervix. *Surg., Gynec. & Obst.*, Oct., 1960, *111*, 493–506. (From: Departments of Obstetrics, Gynecology, and Radiology of the College of Physicians and Surgeons, Columbia University; the Obstetrical, Gynecological and Radiological Service of the Presbyterian Hospital; and the Gynecological and Radiological Service of the Francis Delafield Hospital of Columbia-Presbyterian Medical Center, New York.)

The authors review the complications arising from surgical and radiation therapy for cancer of the cervix in 748 patients who were treated at the Presbyterian and Francis Delafield Hospitals during the years of 1944 to 1957. Because of certain changes which were made in the management of cervical cancer in these hospitals in late 1951 and early 1952, the series is reported in two periods, 1944 to 1951 and 1952 to 1957.

These patients were treated by the following methods: (1) external roentgen rays alone, 82 patients; (2) intracavitary radium and external roentgen rays, 272 patients; (3) radium needles and external roentgen rays, 119 patients; (4) intracavitary radium, external roentgen rays and lymph node dissection, 56 patients; (5) radical operations, 92 patients; (6) radical operations and external roentgen rays, 115 patients; and (7) other, 12 patients. The injuries produced by these methods of therapy were considered in three categories, namely, radiation injuries, surgical injuries and those due to a combination of both.

In reviewing these 748 cases, it appeared that there had been a greater number of fatalities and severe complications in recent years. In the irradiation series two main factors seem responsible: (1) the introduction of the pelvic lymph node dissection after full radiation therapy and (2) the increase in dosage of roentgen therapy. The recognition of these factors resulted in certain changes in the routine of management.

In the patients in whom extensive operation and increased irradiation were combined, these factors were, of course, additive. Preoperative irradiation made the normal tissue less tolerant to operation, and surgical treatment appeared to render tissue more vulnerable to large doses of subsequent irradiation. As a result of the authors' experience with operations performed after roentgen therapy, postirradiation

lymph node dissection has been abandoned in both hospitals.

It has become obvious that treatment with more than 4,000 r in addition to radium, as used with their technique, is hazardous; external irradiation in Stage I and Stage II disease has been reduced to a maximum of 4,000 r tumor dose in four to six weeks with lead shielding in the center of the fields.

An increase in surgical complications in recent years was less apparent; nevertheless, in the earlier period, from 1944 to 1951, there were 12 per cent major complications with no operative mortality and in the latter period 17 per cent major complications and 3 operative deaths. It seemed noteworthy that all of the deaths occurred in patients in whom age or some other constitutional factor had increased the risk. It is the authors' intent to return to a more careful exclusion of the bad risk cases from surgical therapy.—*Ralph M. Scott, M.D.*

Lede, Roberto Enrique. Tratamiento androgenico del carcinoma de mama y embarazo o lactancia, inoperables, agudos, metastasis y recidivas. (Treatment with androgen of acute, inoperable mammary carcinoma associated with pregnancy or lactation, and of metastasis and relapses.) *Prensa méd. argent.*, Mar. 25, 1960, *47*, 764–771. (Address: Rivadavia 4980, Buenos Aires, Argentina.)

In carcinoma of the breast in the first stage (Steinthal's classification), with or without pregnancy, radical mastectomy is recommended, to be followed by roentgen therapy. In the second stage, however, should pregnancy be present, abortion is first performed. In the third stage the pregnancy is also interrupted but, instead of surgery, the patient is subjected to intensive androgen treatment beginning with 100 mg. doses twice daily for five days, then 100 mg. daily for twenty days, then 250 mg. every ten or fifteen days, while roentgen therapy is given. A similar regimen also is advised for cases with "inflammatory" carcinoma, with carcinoma found during the postpartum period, and with metastases or relapses.

In the past four years, the author has seen 56 patients with carcinoma of the breast. When first examined, 24 were Stage I; 20, Stage II; and 12, Stage III. Metastases subsequently were found in 6 of the Stage I group, in 6 of the Stage II group, and in 8 of the Stage III group; relapses occurred in 2 Stage II and 3 Stage III patients.

Treatment with androgen, which has its measure of inconvenience to the patient (virilization), must be carried out to large total doses (up to 8,000 mg.) before it will be really effective. In some cases, though, it permits lengthy, symptom-free survival and consequently deserves to be given a trial when other palliative methods have been unsuccessful.—*E. R. N. Grigg, M.D.*

Uhlmann, Erich M., and Ovadia, Jacques. High-energy electrons in the treatment of malignant tumors of the thorax. *Radiology*, Feb., 1960, *74*, 265–272. (Address: E. M. Uhlmann, Tumor Clinic, Michael Reese Hospital, Chicago 16, Ill.)

Of the malignant neoplasms within the thoracic cage the primary carcinomas of the esophagus and of the bronchus continue to present the highest death rates. Although the absolute number of individuals who have been successfully treated has increased, the five year survival percentage figures have shown little improvement. One of the main problems of radiation therapy has been that the tumor dose of ionizing radiation necessary for control of these neoplasms is so large that it often cannot be tolerated by the afflicted patients. Now, through the modality of high energy electrons, large doses of effective ionizing radiation can be applied to deep-seated tumors with a relatively low integral dose to healthy tissue and consequent good tolerance by the patient.

In the treatment of carcinoma of the esophagus, narrow anterior and posterior fields of varying lengths up to 20 cm. were utilized, and appropriate lucite wedge filters were employed when necessary to produce a more uniform dose. The energy used depended on the anteroposterior diameter of the thoracic cage and was usually in excess of 30 mev. The dose to the spinal column was kept below 4,500 r. Of the 16 patients with carcinoma of the esophagus so treated, 10 received a minimum of 6,000 r to the esophagus, which was considered a satisfactory therapeutic dose. Of the 10 patients who received a full course of therapy, 4 subsequently died, 2 from unrelated causes after two years and one-half year. The 6 living patients have survived for varying periods up to nineteen months. There were no serious complications attributable to the radiation therapy. In the treatment of bronchogenic carcinomas, lucite wedges were also used when necessary to achieve a more uniform dose. Of the 22 patients treated for carcinoma of the bronchus, 17 received a full course of therapy. Of these 17 patients 4 died, with unrelated causes responsible for the death of 2. Of the 13 surviving, 2 have remained free of symptoms for one year, 5 for more than six months, and 6 for less than six months.

The preliminary therapeutic results must be interpreted with the knowledge that none of these patients was operable and that most of them were of advanced age and debilitated by their disease. It is felt that objective evaluation demonstrates the effectiveness of therapy with high energy electrons in these advanced cancers. From experience with electron therapy in other areas of tumors which were less advanced and offered a better prognosis, it is believed that the utilization of high energy electrons in the treatment of earlier diagnosed carcinomas of the esophagus and the bronchus is justified and should

result in a considerably higher five year survival rate than can be achieved at present with conventional methods of radiation therapy and surgery.—*Walter H. Jarvis, Jr., M.D.*

Woodley, R. G., Bronstein, E. L., and Laughlin, J. S. Exit dosimeter for effective patient thickness. *Radiology*, Feb., 1960, *74*, 273–278. (Address: R. G. Woodley, 444 E. 68th St., New York 21, N. Y.)

An adequate radiation treatment plan should give the actual dose distribution at important points within the patient. Usually the treated area is not of homogeneous density and a correction must be applied. One practical and versatile method of making corrections is by an exit dosimeter, where the exit dose from the body or part is measured relative to the maximum dose.

The authors present the design, construction and calibration of such an instrument which consists of a parallel plate ionization chamber with dag-coated polystyrene walls. Exit dose measurements were made in 24 patients and the results are presented in tabular form.

In general, the exit dose measurements are most valuable when the fields are in the region of air-containing lung. An example is given in which a conventional treatment plan would have underestimated the actual tissue dose by 25 per cent.—*Edward B. Best, M.D.*

## RADIOISOTOPES

Werner, S. C., Row, V. V., and Radichevich, I. Nontoxic nodular goiter with formation and release of a compound with the chromatographic mobility characteristics of triiodothyronine. *J. Clin. Endocrinol. & Metabol.*, Oct., 1960, *20*, 1373–1383. (From: Department of Medicine and Biochemistry, Columbia University College of Physicians and Surgeons, and the Presbyterian Hospital in New York, New York.)

Isolated instances have been reported in which l-triiodothyronine has been identified as the major $I^{131}$ labeled iodinated compound in the serum by paper chromatography. The authors report an additional case, that of a fourteen year old girl with a nontoxic goiter of two years' duration.

The history was negative except for a small goiter which had appeared two years before and had enlarged slowly. Administration of l-thyroxine and l-triiodothyronine had apparently arrested the further growth of the goiter. On physical examination the left lobe and isthmus seemed enlarged and the isthmus was cystic to palpation. A bruit was audible in the right supraclavicular area. Initially, while the patient was taking thyroxine, the twenty-four hour $I^{131}$ uptake was 2 per cent and the serum protein iodine was 2.4 μgm. per 100 ml.; butanol-extractable iodine (BEI) was 1.6 μgm. per 100 ml. Three weeks after discontinuation of oral $T_4$ therapy, twenty-four hour thyroidal $I^{131}$ uptake was 22 per cent and a scan showed the activity to be spread diffusely over a right lobe of normal size and over the superior pole of the enlarged left lobe.

Thyroidectomy was performed and the enlarged left lobe was removed. A pathologic diagnosis of nontoxic nodular goiter was returned. Three months postoperatively the patient was euthyroid and the serum protein bound iodine level was 4.0 μgm. per 100 ml.

Chromatographically, approximately 90 per cent of tracer $I^{131}$ activity in venous and arterial blood was present in the iodothyronine fraction, with the $T_3$ area exceeding that of the $T_4$ area in all samples, although $T_4$ accounted for about 30 to 40 per cent of the total distribution. The nodular gland tissue, on the other hand, exhibited almost all of its radioactivity in the $T_3$ area, with no $T_4$. Of the remaining radioactivity 15 per cent was present as MIT and DIT, constituting a reversal of the normal thyronine:thyrosine ratio, which is of the order of 1:8 in the euthyroid gland. In two dimensional chromatograms of the digested nodular tissue the compound termed by the authors $T_3$ migrated as did the stable 1-3-5-3′-$T_3$ which was used as a standard. Its migration was separate from all other compounds.

Preoperatively, and when receiving no medication, the patient had a protein bound iodine level of 4.7 μgm. per 100 ml., of which approximately 2.3 μgm. per 100 ml. was present as $T_3$. Since l-triiodothyronine has been estimated in man to have roughly 45 times the activity of $T_4$, the authors estimate that a thyroxine level equivalent to 9 to 11 μgm. per 100 ml. might have been present. Since the patient was not hyperthyroid and the thyroid was not turning over radioiodine unduly rapidly, it was suspected that the compound identified chromatographically as $T_3$ might not be the naturally occurring form, 1-3-5-3′, but an analogue, such as the d-form, the reverse form (1-3-3′-5′), diiodothyronine ($T_2$) or a conjugate. It is suggested that these compounds could not be distinguished from l-$T_3$ by the usual chromatographic procedures.

Further chromatographic analysis served to eliminate all of these possibilities except the d-form of $T_3$, a phenomenon not heretofore described in humans. No definite explanation for the d-form of $T_3$ can be arrived at except for the possibility that there was a localized derangement of thyroid function which resulted in the production of d-amino acids.—*Frederick J. Bonte, M.D.*

Adams, R., Specht, N., and Woodward, I. Labeling of erythrocytes *in vitro* with radioiodine-tagged l-triiodothyronine as an index of thyroid function: an improved hematocrit correction. *J. Clin. Endocrinol. & Metabol.*, Oct., 1960, *20*, 1366–1372. (From: Depart-

ments of Radiology and Internal Medicine, College of Medical Evangelists, Los Angeles, California.)

As a test of thyroid function the *in vitro* labeling of erythrocytes with $I^{131}$ tagged l-triiodothyronine is gaining widespread attention. Because it can be used as a radioiodine test in children and young adults and in pregnant females without the necessity of administering the tracer isotope to the patient, this test is now being examined critically in many laboratories. Recently, a number of suggestions for improvement in technique and calculation have been made including the one by the present authors. They point out that the quantity of radioiodinated $T_3$ is proportional to the product of the reactants, conforming to the law of mass action, with the reactants being the red blood cell mass and the concentration of labeled $T_3$ in the surrounding plasma.

The authors adduce evidence to show that labeled $T_3$ taken up by the red blood cells appears to be approximately proportional to the product of the red blood cell mass and the concentration of $I^{131}$ l-triiodothyronine remaining in the plasma at the end of incubation. It is further pointed out that, in the original method of Hamolsky, correction is made for variation with the hematocrit of the red blood cell mass but not for the level of l-triiodothyronine concentration as influenced by the hematocrit and the transfer of labeled $T_3$ from the plasma to the cells during labeling. It has been shown that the red blood cell uptake as calculated by Hamolsky's method might appear to be in the hypothyroid range because of a low hematocrit, or in the hyperthyroid range in cases of polycythemia. The authors point out that inconsistent results obtained by investigators other than the original team resulted in samples with high or low hematocrits.

Accordingly, the authors propose calculation of results by a method independent of the hematocrit over any reasonable clinical range. The following equation is used to calculate the binding coefficient, $K$:

$$K = \frac{X/A(1-H)}{H(1-X/A)}$$

where $X$ is the quantity of labeled $T_3$ bound by the cells during incubation, $A$ is the total labeled l-triiodothyronine added to the blood sample, and $H$ is the hematocrit.

From their experience thus far, the authors suggest the following ranges for $K$: euthyroid, 0.10–0.18; hypothyroid, 0.06–0.10; and hyperthyroid, 0.18–0.35.

It is further suggested that for reproducible results, all details of labeling and washing should be standardized within a laboratory and that the fewest washings should be employed consistent with adequate removal of plasma, with about three washes appearing to be the optimal procedure.

It is concluded that, because of its relative independence of the hematocrit, the binding coefficient, $K$, is a more reliable index of thyroid function than is the percentage red blood cell uptake per 100 hematocrit commonly employed in this test. The suggestion embodied in this paper is well worth considering.—*Frederick J. Bonte, M.D.*

Crane, C. W., and Neuberger, A. Absorption and elimination of $^{15}N$ after administration of isotopically labelled yeast protein and yeast protein hydrolysate to adult patients with coeliac disease; I. Rate of absorption of $^{15}N$ yeast protein and yeast protein hydrolysate. *Brit. M. J.*, Sept., 1960, *2*, 815–823. (Address: C. W. Crane, Department of Medicine, Queen Elizabeth Hospital, Birmingham 15, England.)

This article records the findings of the rates of absorption after feeding whole yeast protein and hydrolysate labeled with the stable iostope $N^{15}$. The authors have presumed that metabolism proceeds along the same pathways and at the same rate as in normal subjects once the nitrogen is absorbed into the body.

Four patients suffering from adult celiac disease were studied with one normal adult as a control. The yeast protein and yeast protein hydrolysate labeled with the stable isotope were administered to the patients and urine was collected at half hour intervals. The isotope content of the ammonia and urea in the urine and, in a few experiments, that of the urea and amino acids of the venous plasma was measured.

The appearance of the isotope in the various fractions mentioned was considerably delayed as compared to normal subjects. In the case of the whole protein, the maximum amount of the isotope was present two to two and one-half hours after the ingestion of the labeled material, whereas in the normal subjects the maximum was observed at about fifty minutes. With the protein hydrolysate, deviations from normal were more valuable than with the whole protein and, on the whole, were less marked.

The various factors repsonsible for this delay in absorption are considered. The possibility that hypomotility of the small intestine may be partially responsible has not been excluded. The authors conclude, however, that the rate of absorption of peptids and amino acids is reduced in adult celiac disease by a reduction in the effective absorptive surfaces.—*Ralph M. Scott, M.D.*

Stevenson, J. J. Localization of radio-active implants with image intensification and television. *Proc. Roy. Soc. Med.*, Aug., 1960, *53*, 644–645. (From: Royal Marsden Hospital and the Institute of Urology, London, England.)

The author describes the modifications of the

equipment used for the localization of radioactive implants of the pituitary gland at his institution over the last five years, during which time more than 200 patients were so treated.

Initially the localization of the introducing needle and the subsequent implantation were done by means of fluoroscopy in two planes. Because of the disadvantages inherent in this method, image intensification began to be used. Here the detail was satisfactory but surgeons had difficulty in adapting themselves to the use of the viewing attachments.

The problem was solved by the use of an industrial television chain in conjunction with the image amplifier. The camera is smaller and lighter than the reflecting viewer which it replaces. Detail on the television screen in the frontal and sagittal planes is described as being adequate, but not quite as good as with the optical device. The current in the roentgen-ray tube has to be approximately double. Inasmuch as the monitor is placed some distance away from the patient, there is no significant increase in dose to the observers.

The author states that he has found no major disadvantages in its use and the operating time has been speeded up considerably.—*Ralph M. Scott, M.D.*

## MISCELLANEOUS

Hodara, Morris, Friedman, Milton, and Hine, Gerald J. Radiation dosimetry with fluorods (miniature glass rod dosimetry). *Radiology*, Nov., 1959, *73*, 693–706. (Address: M. Hodara, Radiation Therapy Department, Hospital for Joint Diseases, New York 35, N. Y.)

The authors discuss a method of dosimetry utilizing a miniature radiation-sensitive glass rod. This 1 mm.×6 mm. glass rod consists of silver-activated phosphate glass. Following irradiation, some of the silver ions are converted to silver atoms by capturing electrons ejected from the glass by the ionizing radiation. The rods are then irradiated by ultraviolet light, which produces an orange fluorescence from the silver atoms. The number of silver ions converted into atoms can therefore be used as a measure of dose when the fluorod is placed in an ultraviolet fluorimeter, the design of which is described in some detail.

The small dimensions and chemical inertness of the fluorod make it an ideal dosimeter. Some of the characteristic properties of the fluorod dosimeter that have been noted include linearity of response with dose, temperature independence, directionality independence, and a slow fading of fluorescence. Heat treatment for approximately five hours at 400° C. will reduce the dose effect to background level so that the fluorod may be used again. Due to energy dependence, fluorods should be used only for energies higher than 400 kv. peak roentgen rays. Fluorods should not be used with very large fields. When the field size is increased beyond 150 sq. cm., the contribution of scattered radiation increases the readings more rapidly due to enhanced sensitivity of the fluorods to the lower energy scattered radiations.

The dosimetric properties of the fluorod were found to be ideal for *in vivo* dosimeters. When fluorod measurements were compared with ionization chamber measurements of central axis depth dose, entrance and exit dose, tangential beam dose, and rotational therapy, good agreement was found between the two methods. The potential usefulness of the miniature fluorod in clinical radiation therapy at the supervoltage level appears unlimited.—*John S. Alexander, M.D.*

Troup, J. B., and Bickel, W. H. Malignant disease of the extremities treated by exarticulation; analysis of two hundred and sixty-four consecutive cases with survival rates. *J. Bone & Joint Surg.*, Sept., 1960, *42-A*, 1041–1050. (From: Section of Othopaedic Surgery, Mayo Clinic and Mayo Foundation, Rochester, Minn.)

The survival rates in 264 cases of exarticulation for malignant disease are summarized; there was only 1 hospital death.

Five years after surgery, 41.5 per cent of traced patients with hindquarter amputation and 39.6 per cent of traced patients with hip joint disarticulation were living. In some cases amputation was done to relieve intractable pain or a fungating lesion.

Five years after surgery 40.6 per cent of traced patients with forequarter amputation and 19.2 per cent of 25 traced patients with shoulder joint disarticulation were living. Forequarter amputation has superseded shoulder joint disarticulation in soft tissue tumors of the upper extremity.

The common course of soft tissue fibrosarcoma and liposarcoma was successive recurrences at the amputation site with eventual metastases. Fibromyosarcoma has the best prognosis of the soft tissue tumors with 6 of 10 traced patients surviving five years. Chondrosarcoma gave the best prognosis of the bone tumors, while that of osteogenic sarcoma was poor. Eleven of 68 traced patients with osteogenic sarcoma survived more than five years; 21 of 53 traced patients with chondrosarcoma survived more than five years.

Early radical operation gave gratifying results but hindquarter amputation had a poorer prognosis when it followed unsuccessful attempted local resection of bone tumor than when it was done as a primary procedure. The prognosis also was poor when symptoms were present more than three months, when there was surgical intervention without immediate definitive treatment, in cases of extensive local progression and tumors of borderline operability.—*Martha Mottram, M.D.*